TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926478	9999													
R926479	9999													
R926480	1.9	9999												
R926481	1.445	9999												
R926482	1.037	>10												
R926483	9999													
R926484	1.523	9999												
R926485	4.012	9999												
R926486	0.647	7.403												
R926487	0.554	8.867	1.25											
R926488	0.331	>10	0.752											
R926489	1.414	>10												
R926490	1.571	9999												
R926491	1.158	>10												
R926492	0.645	9999												
R926493	0.25	9.181	0.078											
R926494	0.313	9999	0.078											
R926495	0.121	>10	0.078			0.04	9999	0.038	0.056		0.089	0.24	0.077	0.028
R926496	0.571	>10												
R926497	0.138	9999				0.27	9999	0.205						
R926498	0.209	>10							<0.22		0.515	0.995	0.614	<0.22
R926499	0.29	>10												
R926500	0.418	>10												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926501	0.298	>10				0.609	9999	0.645						
R926502	0.483	>10				0.405	9999	0.491						
R926503	0.452	>10												
R926504	0.569	>10												
R926505	0.145	9999							<0.22		<0.22	<0.22	<0.22	<0.22
R926506	0.343	9999												
R926508	0.127	9999				0.065	9999	0.054	0.086		0.107	0.162	0.054	0.026
R926509	1.16	9999												
R926510	0.44	>10												
R926511	0.786	>10												
R926514	9999	9999												
R926516	1	9999												
R926526	9999	9999												
R926527	9999	9999												
R926528	8.75	9999												
R926535	9999	9999												
R926536	9999	9999												
R926555	9999	9999												
R926559	7.7	9999												
R926560	9999	9999												
R926562	9999	9999												
R926563	9999	9999												
R926564	3.75	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926565	0.625	3.3												
R926566	2.73	9999												
R926567	9.3	9999												
R926569	0.61	3.07												
R926571	9999	9999												
R926572	1.8	6.08												
R926574	1.96	2.63												
R926576	9999	9999												
R926579	9999	9999												
R926580	10	9999												
R926582	1.3	9999												
R926583	9999	9999												
R926584	9999	9999												
R926585	9999	9999												
R926586	2.75	9999												
R926587	9999	9999												
R926588	7.85	9999												
R926589	0.325	10												
R926591	2.62	9999												
R926593	0.68	8.3	0.495											
R926594	9999	9999												
R926595	4.85	9999												
R926604	2.85	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926605	2.45	9999												
R926614	0.228	9999												
R926615	0.445	9999												
R926616	0.625	3.25												
R926617	9.45	9999												
R926620	8.35	9999												
R926623	9999	9999												
R926662	9999	9999												
R926663	9999	9999												
R926675	0.63	9999												
R926676	0.76	9999												
R926680	1.71	9999												
R926681	0.775	9999												
R926682	8.41	9999												
R926683	10	9999												
R926688	2.25	>10												
R926690	0.146	>10												
R926696	0.309	>10												
R926698	9999													
R926699	0.76	9999												
R926700	0.157	>10												
R926701	2.2	9999												
R926702	0.886	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926703	0.525	9999												
R926704	0.564	9999												
R926705	0.263	9999	0.533											
R926706	0.07	2.406	0.078											
R926707	0.214	9999							<0.056		<0.056	0.39	0.088	<0.056
R926708	0.472	9999												
R926709	0.858	9999												
R926710	1.763	9999												
R926711	1.245	9999												
R926712	1.084	9999												
R926713	0.446	8.741												
R926714	0.428	>10												
R926715	0.588	>10												
R926716	1.06	9999												
R926717	7.874	9999												
R926718	1.826	9999												
R926719	0.1335	4.024												
R926720	1.555	9999												
R926721	4.441	9999												
R926722	5.96	9999												
R926723	2.591	9999												
R926724	2.059	9999												
R926725	0.431	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926726	9999	9999												
R926727	0.387	9999												
R926728	0.482	>10												
R926730	0.251	9999												
R926731	9999	9999												
R926732	0.444	9999												
R926733	1.496	9999												
R926734	4.493	9999												
R926735	3.712	9999												
R926736	0.288	9999												
R926737	0.059	9999							0.075		0.073	0.046	0.068	0.017
R926738	0.342	9999												
R926739	0.508	9999												
R926740	4.422	9999												
R926741	2.908	9999							0.961		1.025	9999	0.772	0.537
R926742	0.127					0.043	9999	0.055	0.041		0.055	0.105	0.053	0.022
R926743	9999													
R926744	9999													
R926745	0.083	9999												
R926746	0.989	9999												
R926747	0.213	>10												
R926748	0.345	>10												
R926749	0.472	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926750	0.361	>10												
R926751	0.598	9999												
R926764	0.252	5.64												
R926765	0.324	4.39												
R926766	0.756	9999												
R926767	0.387	>10												
R926768	0.443	>10												
R926769	1.067	9999												
R926770	0.583	9999												
R926771	2.049	9999												
R926772	0.337	7.501												
R926773	0.548	7.849												
R926774	1.934	7.935												
R926775	3.47	>10												
R926776	0.81	9999												
R926777	0.378	9999												
R926778	0.414	9999												
R926779	9999	9999												
R926780	0.152	>10							<0.22		<0.22	0.461	<0.22	<0.22
R926781	0.573	9999												
R926782	0.173	>10							<0.22		<0.22	1.461	0.276	<0.22
R926783	0.304	>10												
R926784	0.252	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926785	0.222	>10							0.989		0.561	1.411	1.312	0.513
R926786	0.504	9999												
R926787	5.422	9999												
R926788	0.336	6.341												
R926789	2.315	9999												
R926790	0.462	7.412												
R926791	0.233	>10							0.064		<0.056	0.896	0.205	<0.056
R926792	3.197	9999												
R926793	3.073	9999												
R926795	2.041	>10												
R926796	0.914	9999												
R926797	2.235	9999												
R926798	2.347	5.87												
R926799	9999	9999												
R926800	4.581	9999												
R926801	10	9999												
R926802	1.251	>10												
R926803	1.541	>10												
R926804	1.578	7.109												
R926805	0.764	9999												
R926806	0.374	9999												
R926807	0.291	9999												
R926808	0.368	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926809	0.78	3.052												
R926810	1.221	9999												
R926811	3.662	9999												
R926812	0.185	>10												
R926813	0.152	9999												
R926814	1.101	9999												
R926815	1.181	9999												
R926816	0.084	9999												
R935000	9999	9999												
R935001	9999	9999												
R935002	9999	9999												
R935003	9999	9999												
R935004	9999	9999												
R935005	9999	9999												
R935006	10	9.8												
R935016	9999	9999												
R935019	8.8	9999												
R935020	9999	9999												
R935021	9999	9999												
R935023	9999	9999												
R935025	1.04	9999												
R935029	2.83	9999												
R935075	0.93	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935076	4.15	9999												
R935077	9999	9999												
R935114	1.725	9999												
R935117	9999													
R935134	0.909	1.799												
R935135	10	9999												
R935136	0.952	2.129												
R935137	10	9999												
R935138	0.096	0.552							<0.22		<0.22	0.373	0.409	<0.22
R935139	0.846	9999												
R935140	0.275	0.959												
R935141	0.727	>10												
R935142	0.873	>10												
R935143	0.573	>10												
R935144	0.63	9999												
R935145	0.548	>10												
R935146	3.802	9999												
R935147	1.404	9999												
R935148	2.218	9.423												
R935149	0.708	>10												
R935150	1.926	9.738												
R935151	0.479	>10												
R935152	0.505	9.316												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935153	0.238	>10												
R935154	0.127	>10							0.104		0.085	0.547	0.131	0.041
R935155	0.401	9999												
R935156	0.149	>10							<0.22		<0.22	0.433	0.22	<0.22
R935157	0.256	4.656												
R935158	0.551	>10												
R935159	0.232	4.135												
R935160	0.202	>10							<0.22		0.317	0.876	0.484	<0.22
R935161	0.277	9999												
R935162	0.269	>10												
R935163	9999	9999												
R935164	0.204	9999												
R935165	4.988	9999												
R935166	0.568	9999												
R935167	2.132	>10												
R935168	0.488	9.484												
R935169	0.999	8.007												
R935170	0.673	9999												
R935171	0.536	9999												
R935172	1.385	6.808												
R935173	0.454	>10												
R935174	1.384	9999												
R935175	0.885	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935176	1.169	9999												
R935177	0.889	>10												
R935178	0.515	9999												
R935179	0.557	9999												
R935180	1.22	9999												
R935181	1.76	9999												
R935182	0.124	2.469												
R935183	0.729	9999												
R935184	0.605	9999												
R935185	0.351	6.642												
R935186	0.211	9999												
R935187	9.059	>10												
R935188	0.239	9999												
R935189	0.619	9999												
R935190	0.156	9999												
R935191	0.151	9999							0.068		0.043	0.213	0.071	0.027
R935192	0.337	9999												
R935193	0.136	9999							0.08		0.048	0.312	0.092	0.037
R935194	0.11	9999							0.125		0.054	0.493	0.118	0.034
R935196	0.117	9999												
R935197	0.174	>10												
R935198	0.126	>10												
R935199	0.45	>10												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935202	0.181	9.765												
R935203	0.562	>10												
R935204	0.554	9999												
R935205	2.959	9999												
R935206	4.711	9999												
R935207	9999	9999												
R935208	1.274	9999												
R935209	0.526	1.035												
R935211	1.238	9999												
R935212	1.427	9999												
R935213	0.619	10												
R935214	0.453	5.499												
R935218	4.712	9999												
R935219	5.409	9999												
R935220	3.789	9999												
R940089	9999	9999												
R940090	9999	9999												
R940095	9999	9999												
R940100	9999	9999												
R940215	0.845	9999												
R940216	0.2675	7.3												
R940217	9999	9999												
R940222	9999	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940233	0.132	>10												
R940235	0.8	>10												
R940250														
R940251														
R940253	1.006	>10												
R940254	0.986	9999												
R940255	1.033	9999												
R940256	1.104	9999												
R940257	0.667	9999												
R940258	0.473	5.72												
R940260	1.126	9999												
R940261	9999	9999												
R940262	9999	9999												
R940263	9999	9999												
R940264	10	9999												
R940265	0.239	>10							0.981		0.306	1.211	1.131	0.486
R940266	9999	9999												
R940267	3.151	9999												
R940269	1.654	9999												
R940270	2.144	8.739												
R940271	0.401	6.821												
R940275	0.862	9999												
R940276	0.211	9999							0.136		0.073	0.332	0.251	<0.056

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940277	0.141	9999							0.279		0.315	0.625	0.262	0.181
R940280	6.999	9999												
R940281	0.525	5.529												
R940282	0.401	3.015												
R940283	0.553	4.982												
R940284	0.465	3.744												
R940285	3.499	9999												
R940286	0.337	7.082												
R940287	0.288	7.684												
R940288	0.208	9999												
R940289	0.272	9999												
R940290	0.116	9999							0.255		0.545	0.59	0.246	0.1
R940291	0.396	9999												
R940292	0.683	9999												
R940293	9999	9999												
R940294	1.366	9999												
R940295	0.126	8.812												
R940296	0.41	>10												
R940297	3.465	10												
R945025	9999	9999												
R945032	0.37	9999												
R945033	9999	9999												
R945034	1.85	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945035	9999	9999												
R945036	9999	9999												
R945037	9999	9999												
R945038	9999	9999												
R945040	9999	9999												
R945041	9999	9999												
R945042	9999	9999												
R945043	9999	9999												
R945045	9999	9999												
R945046	0.82	>10												
R945047	0.845	9999												
R945048	0.76	9999												
R945051	0.95	>10												
R945052	0.425	2.48												
R945053	0.1185	1.48												
R945056	10	9999												
R945057	10	9999												
R945060	0.9375	>10												
R945061	10	9999												
R945062	0.625	>10												
R945063	1.55	>10												
R945064	0.53	>10												
R945065	1.425	>10												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945066	5.2	nd												
R945067	9999	nd												
R945068	9999	nd												
R945070	0.45	>10												
R945071	0.205	>10												
R945096	1.75	>10												
R945097	10	9999												
R945109	1.025	>10												
R945110	0.602	9999												
R945117	4.077	9999												
R945118	0.668	9999												
R945124	0.69	7.852												
R945125	0.896	>10												
R945126	9999	9999												
R945127	0.704	8.955												
R945128	0.685	8.8												
R945129	1.003	>10												
R945130	1.874	9999												
R945131	0.77	9999												
R945132	0.571	8.77												
R945133	1.064	>10												
R945134	9999	9999												
R945135	0.986	8.245												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945137	1.649	>10												
R945138	1.058	6.733												
R945139	1.016	>10												
R945140	0.573	>10												
R945142	1.049	>10												
R945144	0.244	9999												
R945145	9999	>10												
R945146	3.756	9999												
R945147	3.546	9999												
R945148	0.307	9999												
R945149	0.391	>10												
R945150	0.467	>10							>2		>2	9999	0.709	0.634
R945151	4.07	9999												
R945152	6.94	9999												
R945153	0.688	6.561												
R945155	1.878	>10												
R945156	0.787	9999												
R945157	1.477	9999												
R945162	9999	9999												
R945163	0.922	4.251												
R945164	10	9999												
R945165	9999	9999												
R945166	9999	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R945167	0.761	9999												
R945168	10	9999												
R945169	10	9999												
R945170	0.661	>10												
R945171	1.327	9999												
R945172	1.179	9999												
R945173	1.419	9999												
R945175	1.648	9999												
R950082	9999	9999												
R950083	9999	9999												
R950090	9999	9999												
R921302	0.37	9999				0.19	9999	0.282						
R950092	9999	9999												
R950093	0.64	5.55												
R950100	0.71	>10												
R950107	0.46	>10												
R950108	2.075	>10												
R950109	7.95													
R950120	3	9999												
R950121	4.25	>10												
R950122	3.025	9999												
R950123	3.25	8.45												
R950125	1.375	6.3												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950129	0.665	>10												
R950130	4.9													
R950131	9999													
R950132	9													
R950133	2.2	>10												
R950134	1.875	9999												
R950135	0.85	>10												
R950137	2.23	9999												
R950138	9.5													
R950139	1.375	9999												
R950140	2.825	9999												
R950141	0.31	>10												
R950142	10													
R950143	8.23													
R950144	10													
R950145	9999													
R950146	9999													
R950147	9999													
R950148	2.275	9999												
R950149	10	9999												
R950150	9999	9999												
R950151	9999													
R950152	10													

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950153	9999													
R950154	2.075	9999												
R950155	9999													
R950156	9999													
R950157	9999													
R950158	9.98													
R950159	0.61	9999												
R950160	1	9999												
R950162	0.434	>10												
R950163	0.874	9999												
R950164	1.893	9999												
R950165	1.288	9999												
R950166	1.889	9999												
R950167	9999	9999												
R950168	6.496	8.653												
R950169	1.273	9.518												
R950170	9999	9999												
R950171	0.585	>10												
R950172	0.983	9999												
R950173	2.368	>10												
R950174	4.618	9999												
R950175	1.688	9999												
R950176	1.342	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950177	2.361	8.434												
R950178	0.688	>10												
R950179	0.955	>10												
R950180	0.278	9999												
R950181	0.254	9999												
R950182	0.627	9999												
R950183	4.797	9999												
R950184	2.222	9999												
R950185	1.03	8.81												
R950186	0.558	>10												
R950187	0.724	>10												
R950188	2.327	9999												
R950189	10	9999												
R950190	1.573	9999												
R950191	0.178	9999							<0.22		>2	0.401	<0.22	<0.22
R950192	0.244	9999												
R950193	0.61	9999												
R950194	2.04	9999												
R950195	0.473	9999												
R950196	2.2	9999												
R950197	0.531	9999												
R950198	0.406	>10												
R950199	0.408	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950200	0.245	9999												
R950201	0.261	9999												
R950202	3.218	9999												
R950203	9.035	9999												
R950204	6.285	9999												
R950205	8.997	9999												
R950206	3.66	>10												
R950207	0.164	9999							<0.22		<0.22	0.288	<0.22	<0.22
R950208	0.267	9999												
R950209	0.748	9999												
R950210	10	9999												
R950211	10	9999												
R950212	0.253	9999												
R950213	9999	9999												
R950214	10	9999												
R950215	0.409	9999												
R950216	0.327	9999												
R950217	0.34	9999												
R950218	0.292	9999												
R950219	0.439	9999												
R950220	0.489	9999												
R950221	0.636	9999												
R950222	0.865	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950223	0.763	9999												
R950224	0.687	9999												
R950225	5.283	9999												
R950226	1.374	9999												
R950227	1.029	9999												
R950229	0.98	9999												
R950230	7.91	9999												
R950231	1.968	9999												
R950232	10	9999												
R950233	0.98	9999												
R950234	10	9999												
R950235	4.095	9999												
R950236	0.955	9999												
R950237	9999	9999												
R950238	10	9999												
R950239	2.063	9999												
R950240	1.766	9999												
R950241	3.275	9999												
R950251	9999	9999												
R950253	0.697	9999												
R950254	0.496	9999												
R950255	10	9999												
R908698	1.67	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R908699	0.217	9999												
R908700	1.273	9999												
R908701	0.099	7.643												
R908702	0.104	7.395												
R908703	0.63	9999												
R908704	0.511	9999												
R908705	0.801	9999												
R908706	0.445	9999												
R908707	1.834	9999												
R908709	2.414													
R908710	1.838	99												
R908711	1.761													
R908712	0.075	99												
R908734	1.379													
R909255	0.244	9999												
R909259	0.43	9999												
R909260	1.041	9999												
R909261	0.93	9999												
R909263	0.289	9999												
R909264														
R909265	99													
R909266	99													
R909267	0.589	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R909268	0.071	9999												
R909290	0.226													
R909292	1.172													
R909308	0.671	9999												
R909309	0.083	9999												
R920394														
R920395	0.092	9999												
R920396														
R920397														
R920398														
R920399														
R920404														
R920405														
R920406														
R920407														
R920408														
R920410	0.125	9999												
R920411	0.564	9999												
R925745	1.766	9999												
R926238	9999													
R926752	0.338	9999												
R926753	0.108	9999												
R926754	0.388	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926755	1.693	9999												
R926756	1.365	9999												
R926757	0.158	9999												
R926759	0.688	9999												
R926760	2.893	9999												
R926761	0.245	9999												
R926762	0.386	9999												
R926763	0.195	9999												
R926794	1.382	9999												
R926826	0.613	9999												
R926827	1.098	9999												
R926828	0.306	9999												
R926829	0.688	9999												
R926830	0.569	10												
R926831	0.133	10												
R926832	0.365	9999												
R926833	1.129	9999												
R926834	0.145	9999												
R926835	0.296	9999												
R926836	10	9999												
R926837	2.994	9999												
R926838	0.583	9999												
R926839	0.161	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926840	1.1	9999												
R926841	0.551	9999												
R926842	7.733	9999												
R926843	7.371	9999												
R926844	1.1	9999												
R926845	2.558	7.812												
R926846	0.86	6.264												
R926847	1.479	6.264												
R926848	0.254	10												
R926851	0.446													
R926855	9999	9999												
R926856	0.734	9999												
R926857	1.209	9999												
R926859														
R926860	1.949	99												
R926862	0.774	9999												
R926863														
R926866														
R926870	3.294													
R926871	2.146													
R926874	0.638	9999												
R926879	0.397	9999												
R926880														

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926881														
R926883														
R926885														
R926886														
R926887	1.747													
R926890	0.361	9999												
R926891	0.152	9999												
R926892	0.685	9999												
R926893	10	9999												
R926894	9999	9999												
R926895	0.339	9999												
R926896	1.622	9999												
R926897	1.727	9999												
R926898	1.1	9999												
R926899	1.1	9999												
R926900	9999	9999												
R926902	1.37	4.586												
R926903	0.243	9999												
R926904	0.538													
R926905	99													
R926906	0.794													
R926907	0.764													
R926908	0.585													

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926909	0.379													
R926913	0.548	9999												
R926914	1.86	9999												
R926915	1.713	9999												
R926916	1.958	9999												
R926917	1.169	9999												
R926918	2.521	9999												
R926919	1.413	9999												
R926922	0.305	9999												
R926923	0.346	9999												
R926925	0.307	99												
R926926	0.401	9999												
R926927	0.348	9999												
R926928	0.575	9999												
R926929	1.916	9999												
R926930	99	9999												
R926931														
R926932	0.31	9999												
R926933														
R926934														
R926935	4.44													
R926936														
R926937														

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926938														
R926939	3.615													
R926940	7.754													
R926941	4.195													
R926942	4.81													
R926943														
R926944	0.225	99												
R926945	0.457	9999												
R926946														
R926947	0.354	9999												
R926948	0.246	9999												
R926949	0.089	9999												
R926950	99	9999												
R926951	0.183	9999												
R926953	0.049	9999												
R926954	0.284	9999												
R926955	0.36	9999												
R926956	0.211	9999												
R927016	1.408													
R927017	2.449													
R927018	1.446													
R927019	1.179													
R927020	1.316	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R927023	0.918	9999												
R935221	9999	9999												
R935222	0.52	9999												
R935223	0.469	9999												
R935224	4.578	9999												
R935225	6.495	9999												
R935237	0.24	9999												
R935238	1.854	9999												
R935239	0.609	9999												
R935240	0.606	9999												
R935242	2.855	9999												
R935248	1.1	9999												
R935249	1.1	9999												
R935250	1.1	9999												
R935251														
R935252														
R935253														
R935255	0.374	9999												
R935256	0.324	9999												
R935258	1.191	9999												
R935259	1.777	9999												
R935261	0.391	9999												
R935262	0.516	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935263	0.106	10												
R935264	0.135	9999												
R935266	2.97													
R935267	2.463													
R935268	1.059													
R935269	1.715													
R935271														
R935276	2.33													
R935277	22.883	8.9												
R935278	4.753	9999												
R935279	0.889	9999												
R935280	99													
R935281	1.399	9999												
R935286	1.158	9999												
R935287	0.403	9999												
R935288	1.58	9999												
R935289	1.688	9999												
R935290	0.34	9999												
R935291	1.364	9999												
R935292	0.483	9999												
R935293	0.141	9999												
R935294	0.388	9999												
R935295	1.943	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935296	99	9999												
R935297	7.328	9999												
R935298	0.252	99												
R935299	0.21	9999												
R935300	0.243	9999												
R935301	4.05	99												
R935302	0.189	9999												
R935303	0.244	99												
R935304	0.188	9999												
R935305	0.495	9999												
R935306	0.345	99												
R935307	0.139	99												
R935308	0.275	9999												
R935309														
R935310														
R935320	2.769													
R935321	2.986													
R935322	3.416													
R935323	9999													
R935324	9999													
R935336	0.341	9999												
R935337	9999													
R935338	0.411	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R935339	9999													
R935340	3.606													
R935351	9999	9999												
R935352														
R935353	9999	9999												
R935354	99	9999												
R935355	9999	9999												
R935356	99													
R935357	99	9999												
R935358	9999	9999												
R935359	1.027	9999												
R935360	0.903	9999												
R935361	1.438	9999												
R935362	0.409	9999												
R935363	0.405	9999												
R935364	0.563	9999												
R935365	0.373	9999												
R935366	0.216	9999												
R935367	0.053	9999												
R940079	9999													
R940110	9999	9999												
R940299	2.497	9999												
R940300	10	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940301	1.975	9999												
R940304	9999	9999												
R940306	1.1	9999												
R940307	0.291	9999												
R940308	0.612	4.168												
R940309	1.132	9999												
R940311	1.95													
R940312	2.557													
R940314	4.197													
R940316	1.858													
R940317	0.913	9999												
R940318	3.792													
R940319	9999													
R940321	9999													
R940323	0.048	9999												
R940337	1.098													
R940338	0.073	9999												
R921303	0.033	99												
R940345	1.712													
R940346	0.142	99												
R940347	0.063	99												
R940348	2.189													
R940349	0.044	7.4												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R940350	0.092	4												
R940351	0.12	2.7												
R940352	0.101	9999												
R940353	0.091	9999												
R940354	0.115	99												
R945236	0.562	9999												
R945237	0.461	9999												
R945242	0.247	9999												
R945263	1.642													
R921304	0.085	9999												
R945299														
R950244	9999													
R950245	9999													
R950246	9999													
R950247	9999													
R950261	0.611	9999												
R950262	0.285	9999												
R950263	0.284	3.299												
R950264	0.198	9999												
R950265	0.312	9999												
R950266	0.645	9999												
R950267	0.18	9999												
R950290	9999	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950291	9999	9999												
R950293	3.689	8.155												
R950294	2.005	8.005												
R950295	2.041	8.795												
R950296	0.495	9999												
R950344	99													
R950345	1.962	99												
R950346	0.345	9999												
R950347	0.548													
R950348	0.066													
R950349	0.078	9999												
R950356														
R950368	0.038	9999												
R950371														
R950372	1.348	9999												
R950373														
R950374	0.599	9999												
R950376	2.539													
R950377	99													
R950378														
R950379	0.545	9999												
R950380	3	9999												
R950381	0.11	99												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R950382														
R950383	0.114	9999												
R950385														
R950386	0.973													
R950388	2.518													
R950389	0.612	9999												
R950391	999	9999												
R950392	0.956	9999												
R950393	0.404	9999												
R945028														
R935241														
R940298														
R940302														
R940303														
R940305														
R935260	9999													
R909258														
R940313	9999													
R940315	9999													
R935275	9999													
R940320	9999													
R940322	9999	9999												
R926910	9999	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R926911	9999	9999												
R926912	9999	9999												
R926853	9999	9999												
R926852	9999	9999												
R926854	9999	9999												
R926920	9999	9999												
R926921	99	9999												
R926924	99	9999												
R926858														
R926861	9999	9999												
R945298	9999	9999												
R940328	9999													
R926869														
R926873	9999													
R926875	9999													
R926876	9999													
R926877	9999													
R940336	9999													
R926878	9999													
R926882	9999													
R926884	9999													
R926889	9999													
R920400	9999													

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R920401	9999													
R920402	9999													
R920403	9999													
R940342	99													
R920409	9999													
R940344	9999													
R926888	9999													
R926758														
R927024	0.326	99												
R927025	0.326													
R927026	9999	9999												
R927027	9999	9999												
R927028	0.208	9999												
R927029														
R927030	0.26	9999												
R927031	0.215	99												
R927032	0.899													
R927035	0.583	9999												
R927036														
R927037	0.233	9999												
R927038	1.05	9999												
R927039	1.23	9999												
R927040	1.05	9999												

TABLE 1

Test Compound	Low Density			CHMC anti-IgE Hexos.	CHMC Ionomycin Hexos.	Basophils anti-IgE Histamine	Basophils Ionomycin Histamine	Basophils Dust mite Histamine	High Density					
	CHMC anti-IgE Tryptase	CHMC Ionomycin Tryptase	CHMC anti-IgE LTC4						BMMC anti-IgE hexos	BMMC Ionomycin Hexos.	BMMC anti-IgE histamine	BMMC anti-IgE LTC4	BMMC anti-IgE TNF-alpha	BMMC anti-IgE IL-6
R927041	0.788	9999												
R927042														
R935270														
R935368	0.082	9999												
R935369	0.255	9999												
R935370														
R935371	0.794	9999												
R935372	0.06	9999												
R935373	0.274	9999												
R935374	0.356	9999												
R935375	10	9999												
R935376														
R935377														
R935378	0.566	9999												
R935379														
R935380	1.61	99												

TABLE 2

	High Density									
	CHMC high density hexos	CHMC high density tryptase	CHMC high density histamine	CHMC high density LTC4	CHMC high density TNF-alpha	CHMC high density IL-13	Toxicity Jurkat Light Scat.	Toxicity Jurkat Cell Titer Glo	Toxicity BJAB Light Scat.	Toxicity BJAB Cell Titer Glo
R008951										
R008952										
R008953										
R008955										
R008956										
R008958										
R067934										
R067963										
R070153										
R070791										
R081166										
R088814										
R088815										
R091880										
R092788							9999		9999	
R909241								3.736		
R921219	0.124	0.121	0.162	0.034	0.190	0.175		>10		>10
R925775							9999		9999	
R925778							9999		9999	
R925779							>10		9999	
R925797							>10		9999	
R926108							>10		>10	
R926109	0.783	0.906	1.827	0.808	1.504	1.664	>10		9999	

TABLE 2

	High Density									
	CHMC high density hexos	CHMC high density tryptase	CHMC high density histamine	CHMC high density LTC4	CHMC high density TNF-alpha	CHMC high density IL-13	Toxicity Jurkat Light Scat.	Toxicity Jurkat Cell Titer Glo	Toxicity BJAB Light Scat.	Toxicity BJAB Cell Titer Glo
R926110							>10		>10	
R921218	0.464	0.647	0.463	0.695	1.752	2.0776	>10		>10	
R926113	1.448	1.649	1.848	0.468	5.678	3.569	>10		>10	
R926146							9999		9999	
R926210							>10		9999	
R926240							10		9999	
R926248							>10		9999	
R926249							>10		9999	
R926253							9999		9999	
R926256							>10		9999	
R926258							9999		9999	
R926387							>10		9999	
R926395							>10		9999	
R926396							>10		9999	
R926411							8.5		>10	
R926486	1.088	1.313	1.928	0.834	0.455					
R926488	0.521	0.623	0.792	0.201	2.443	1.012				
R926493	0.889	1.093	1.324	0.474	>2			>4.33		
R926494	0.640	>2	9999	0.326	9999					
R926495	0.100	0.235	0.066	0.241	0.362	0.449		>10		>10
R926496	0.429	0.533	0.809	0.414	0.622					
R926497	1.106	1.234	1.333		1.876	9999				
R926501	>2	>2	9999		9999	9999		>4.33		>4.33

TABLE 2

	High Density						Toxicity Jurkat Light Scat.	Toxicity Jurkat Cell Titer Glo	Toxicity BJAB Light Scat.	Toxicity BJAB Cell Titer Glo
	CHMC high density hexos	CHMC high density tryptase	CHMC high density histamine	CHMC high density LTC4	CHMC high density TNF-alpha	CHMC high density IL-13				
R926502	>2	>2	>2		1.807	>2		1.513		
R926505								4.199		
R926508	0.170	0.434	0.105		0.505	0.763		>10		>10
R926510	0.921	1.115	1.667		0.417	0.686		2.77		
R926511	1.183	1.474	1.73		1.307	>2		>4.33		>4.33
R926614	>10	>10			>10	6.442				
R926696	<1.1	<1.1	<1.1	<1.1	<1.1	1.773		>5.0		
R926699	<1.1	<1.1	1.44	<1.1	<1.1	1.294				
R926700	<1.1	<1.1	<1.1	<1.1	<1.1	2.053				
R926703	1.512	1.947	>2	0.724	>2					
R926704	>2	9999	9999	9999	9999					
R926705	1.007	1.256	0.641	0.494	9999					
R926706	>2	9999	9999	1.491	9999					
R926742	0.104	0.217	0.080		0.385	0.667		9		>10
R926745								>10		>10
R926780								>5.0		
R926782								>4.33		>4.33
R935075	0.647	1.212	0.443	<0.22	>2			>4.33		>4.33
R935154								>4.33		
R935156								4.054		
R940216	<1.1	<1.1	1.176	<1.1	3.188	3.006				
R940233	0.577	0.642	0.586	0.118	2.247	1.781		>4.33		>4.33
R945032	0.357	0.458	0.439	0.0929	1.082	0.291				

TABLE 2

	High Density						Toxicity Jurkat Light Scat.	Toxicity Jurkat Cell Titer Glo	Toxicity BJAB Light Scat.	Toxicity BJAB Cell Titer Glo
	CHMC high density hexos	CHMC high density tryptase	CHMC high density histamine	CHMC high density LTC4	CHMC high density TNF-alpha	CHMC high density IL-13				
R945033	8.151	8.868			>10	5.983				
R945071	<1.1	<1.1	<1.1	<1.1	<1.1	<1.1				
R945128	1.279	1.749	0.547	0.729	>2	ND				
R945140	0.994	1.112	1.551		1.714	9999				
R945142	>2	>2	9999		>2	9999				
R945150								>4.33		>4.33
R921302	0.682	0.795	1.588	0.514	1.173	1.672				
R950141	0.567	0.618	0.627	0.201	1.059	0.798				
R950207								>4.33		

7.7 The 2,4-Pyrimidinediamine Compounds of the Invention Selectively Inhibit the Upstream IgE Receptor Cascade

To confirm that many of the 2,4-pyrimidinediamine compounds of the invention exert their inhibitory activity by blocking or inhibiting the early IgE receptor signal transduction cascade, several of the compounds were tested in cellular assays for ionomycin-induced degranulation, as described below.

7.7.1 CHMC Low Cell Density Ionomycin Activation: Tryptase Assay

Assays for ionomycin-induced mast cell degranulation were carried out as described for the CHMC Low Density IgE Activation assays (Section 6.4.3, *supra*), with the exception that during the 1 hour incubation, 6X ionomycin solution [5mM ionomycin (Signma I-0634) in MeOH (stock) diluted 1:416.7 in MT buffer (2 μM final)] was prepared and cells were stimulated by adding 25 μl of the 6X ionomycin solution to the appropriate plates.

7.7.2 Basophil Ionomycin Activation: Histamine Release Assay

Assays for ionomycin-induced basophil cell degranulation were carried out as described for the Basophil IgE or Dustmite Activation Assay (Section 6.4.6, *supra*), with the exception that following incubation with compound, cells were stimulated with 20 μl of 2 μM ionomycin.

7.7.3 Results

The results of the ionomycin-induced degranulation assays, reported as IC_{50} values (in μM) are provided in TABLE 1, *supra*. Of the active compounds tested (*i.e.*, those that inhibit IgE-induced degranulation), the vast majority do not inhibit ionomycin-induced degranulation, confirming that these active compounds selectively inhibit the early (or upstream) IgE receptor signal transduction cascade.

These results were confirmed for certain compounds by measuring anti-IgE-induced and ionomycin-induced calcium ion flux in CHMC cells. In these Ca^{2+} flux tests, 10 μM R921218 and 10 μM R902420 inhibited anti-IgE-induced Ca^{2+} flux, but had no effect on ionomycin-induced Ca^{2+} flux (See FIG. 4).

7.8 The Inhibitory Effect of the 2,4-Pyrimidinediamine Compounds of the Invention is Immediate

To test the immediacy of their inhibitory effect, certain 2,4-pyrimidinediamines of the invention were added simultaneously with anti-IgE antibody activator in the cellular assays described above. All compounds tested blocked IgE-induced degranulation of CHMC cells to the same extent as observed when the compounds were pre-incubated with CHMC cells for 10 or 30 min. prior to receptor cross-linking.

7.9 Kinetics of Pharmacological Activity *In vitro*

Compounds R921218, R921302, R921219, R926240, R940277, R926742, R926495, R909243 and R926782 were tested in washout experiments. In the experiments, CHMC cells were either activated immediately with anti-IgE antibody in the presence of 1.25 μM compound (time zero), or the compound was washed out followed by activation with anti-IgE antibody at 30, 60 or 120 min. The inhibitory activity of these compounds was greatly diminished 30 min. after compound removal, indicating that constant exposure of mast cells to these compounds is required for maximal inhibition of degranulation The other compounds tested yielded similar results.

7.10 Toxicity: T- and B-Cells

The ability of the compounds of the invention to exert their inhibitory activity without being toxic to cells of the immune system was demonstrated in cellular assays with B- and T-cells. The protocols for the assays are provided below.

7.10.1 Jurkat (T-Cell) Toxicity

Dilute Jurkat cells to $2x10^5$ cells/ml in complete RPMI (10% heat-inactivated fetal bovine serum) media and incubate at 37°C, 5% CO_2 for 18 hours. Add 65 ul cells at 7.7×10^5 cells/ml to a 96-well V-bottom plate (TC-treated, Costar) containing 65 ul 2X compound (final vehicle concentration is 0.5% DMSO, 1.5% MeOH). Mix, incubate plates for 18-24 hr at 37°C, 5% CO_2. Toxicity was assessed by flow cytometric analysis of cellular light scatter

7.10.2 BJAB (B-Cell) Toxicity

The B-cell line BJAB was cultured in log phase in RPMI1640 + 10% heat-inactivated fetal bovine serum, 1x L-glutamine, 1x penicillin, 1x streptavidin and 1x beta-

mercaptoethanol at 37°C, 5% CO2. First, BJABs were harvested, spun and resuspended in culture medium to a concentration of $7.7x10^5$ cells/mL. 65uL cells were mixed with 65 uL compound, in duplicate and in the presence of 0.1% DMSO in a V-bottomed 96-well tissue culture plate. Cells were incubated with compound at various dilutions at 37°C, 5% CO_2. Toxicity was assessed by flow cytometric analysis of cellular light scatter.

7.10.3 Toxicity: Cell Titer Glo Assay

Seed 50 µl cells ($1x10^6$/ml) into each well containing 50 µl compound. The final vehicle concentration is 0.5% DMSO, 1.5% MeOH. Shake plates for 1 minute to mix cells and compound. Incubate plates at 37°C (5% CO_2) for 18 hours. Next day, harvest 50 µl cells from each well, add to 50 µl Cell Titer Glo reagent (Invitrogen). Shake plates for 1 minute. Read on luminometer.

7.10.4 Results

The results of the T- and B-cell toxicity assays, reported as IC_{50} values (in µM), are presented in TABLE 2, *supra*. With a few exceptions (see TABLE 1), all compounds tested were non-toxic to both B- and T-cells at effective inhibitory concentrations. Assays performed with primary B-cells yielded similar results.

7.11 The 2,4-Pyrimidine Compounds Are Tolerated In Animals

The ability of the compounds of the invention to exert their inhibitory activity at doeses below those exhibiting toxicity in animals was demonstrated with compounds R921218, R921219 and R921302.

7.11.1 R921218

R921218 was studied in an extensive program of non-clinical safety studies that concluded this agent to be well tolerated in both rodents and non-rodents. To summarize the outcome of toxicology/non-clinical safety testing with R921218; this agent produced no dose limiting toxicity by the intranasal route of administration in non-rodents (rabbits and primates) or by the oral route of administration in rodents (mice and rats) during 14-day repeat-dose toxicity studies at doses many fold above the anticipated dose expected to produce efficacy in man. There were no adverse findings in a core safety pharmacology battery of cardiovascular, respiratory and/or central nervous system function. There was no evidence for mutagenic or clastogenic potential in genetic toxicology testing

nor were there untoward effects after exposure to skin and eyes. A short discussion of key toxicology studies is provided.

A 14-day repeat-dose intranasal toxicity study in Cynomolgus monkeys was performed at doses of 2.1, 4.5 or 6.3 mg/kg/day. In life parameters included: clinical observations, body weights, food consumption, ophthalmology, blood pressure, electrocardiography, hematology, clinical chemistry, urinalysis, immunotoxicological assessment, gross necropsy, organ weights, toxicokinetic assessments and histopathology (including the nasal cavity). There were no adverse findings attributed to R921218 in any study parameter and the NOAEL (no observed adverse effect level) was considered 6.3 mg/kg/day.

A 14-day repeat-dose intranasal toxicity study in New Zealand White rabbits was performed at doses of 1.7, 3.4 or 5.0 mg/kg/day. In life parameters included: clinical observations, body weights, food consumption, ophthalmology, hematology, clinical chemistry, gross necropsy, organ weights, toxicokinetic assessments and histopathology (including the nasal cavity). There were no adverse findings attributed to R921218 in any study parameter and the NOAEL (no observed adverse effect level) was considered 5.0 mg/kg/day.

7.11.2 R921219

In pilot dose finding studies a single dose oral dose of 600 mg/kg was considered a NOEL (no observed effect level) while multiple (7-day) doses of 200 mg/kg/day and above were not tolerated.

In the *in vitro Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay (Ames test), R921219 was found to test positive in tester strain TA1537, with and without metabolic activation, confirming the results of an earlier study. R921219 was not found to adversely affect any of the other 4 tester strains. R921219 was not found to possess clastogenic potential when studied in an *in vitro* chromosomal aberration assay.

7.11.3 R921302

Several non-GLP pilot toxicity studies have been conducted in rodents. In the mouse an oral dose of 1000 mg/kg was tolerated for up to 7-days. In a 14-day oral toxicity study in the mouse was conducted with doses of 100, 300 and 1000 mg/kg. A dose of 1000 mg/kg was not tolerated, while a dose of 300 mg/kg promoted evidence for

histopathological changes in the vulva. A dose of 100 mg/kg was considered the NOAEL (no observed adverse effect level) in the study. A 28-day oral toxicity study in the mouse was conducted at doses of 100 mg/kg q.d., 100 mg/kg b.i.d., 300 mg/kg q.d. and 300 mg/kg b.i.d. R921302 was not tolerated at 300 mg/kg q.d. or b.i.d. The lower doses (100 mg/kg q.d. or b.i.d.) appeared to be well tolerated (results of clinical and histopathology are not yet known). In the rat oral doses of 50, 150 and 300 mg/kg given for 32 days appeared to be well tolerated (results of clinical and histopathology are not yet known).

In the *in vitro Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay (Ames test), R921302 was found to test positive in tester strain TA98 with S9 and TA1537, with and without metabolic activation. R921302 was not found to adversely affect any of the other 3 tester strains. R921302 was not clastogenic when assessed in an *in vitro* chromosomal aberration assay.

7.12 The 2,4-Pyrimidinediamine Compounds Are Orally Bioavailable

Over 50 2,4-pyrimidinediamine compounds of the invention were tested for oral bioavailability. For the study, compounds were dissolved in various vehicles (e.g. PEG 400 solution and CMC suspension) for intravenous and oral dosing in the rats. Following administration of the drug, plasma samples were obtained and extracted. The plasma concentrations of the compounds were determined by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) methods. Pharmacokinetic analyses were performed based on the plasma concentration data. The pharmacokinetic parameters of interest include Clearance (CL), Volume of distribution at steady-state (Vss), terminal half-life ($t_{1/2}$), and oral bioavailability (%F).

These pharmacokinetic studies indicate that many of the 2,4-pyrimidinediamine compounds are orally available, with %F up to approximately 50% (in the range of 0-50%). The half-lives ranged from 0.5 to 3 hr. In particular, Compounds R940350, R935372, R935193, R927050 and R935391 exhibited good oral bioavailabilities and half-lives in rats. Thus, these studies confirm that these 2,4-pyrimidinediamine compounds are suitable for oral administration.

7.13 The Compounds Are Effective for the Treatment of Allergies

The *in vivo* efficacy of compounds R926109, R921218, R921219, R921302, R926495, R926508, R926742, R926745 and R945150 towards allergies was evaluated in

the mouse model of passive cutaneous anaphylaxis (PCA). This model provides a direct measure of IgE-induced degranulation of tissue mast cells. In this model, IgE primed animals are exposed to an allergen challenge, and the change in permeability of dermal vasculature that results from histamine release from mast cells is measured by change in the amount of dye leakage into surrounding tissue. Inhibition of mediator release by compounds that modulate mast cell degranulation is easily measured by extracting the dye from the tissue.

7.13.1 Study Protocol and Results

In the PCA assay mice are passively sensitized by intradermal injection with anti-dinitrophenol (DNP) IgE antibodies (Day –1). At predetermined times animals are treated with the test agent (Day 0). The modulatory effect of the agent on cutaneous mast cell degranulation is measured following intravenous injection of DNP conjugated to human serum albumin (HSA-DNP), together with Evans blue dye. The resulting cross-linking of the IgE receptor and subsequent mast cell degranulation-induced increase in vascular permeability is determined by measuring the amount of dye extravasation into the tissue. Dye is extracted from the tissue by formamide, and the absorbance of this extract is read at 620 nm. The inhibitory effect of drug treatment is reported as the percent inhibition compared to vehicle treatment, that is, the percent reduction in A_{620}.

Two compounds have been tested as positive controls: the histamine antagonist diphenhydramine and the serotonin antagonist cyproheptadine. Both mediators (histamine and serotonin) are released upon IgE-mediated degranulation from the mouse mast cell. Both reference compounds inhibit the PCA response; cyproheptadine was used routinely in subsequent experiements. Cyproheptadine reproducibly inhibited the PCA response by 61% +/- 4% (8 mg/kg, i.p., 30 minutes pretreatment time, n=23 experiments).

7.13.1.1 Results

A dose-dependent inhibition of the FcεR--mediated vascular leakage was observed with increasing doses of R921218, R926109, R921219 and RR921302. These compounds were administered either in a solution formulation (67%PEG/33% citrate buffer) or an aqueous suspension (1.5% Avicel). These results demonstrate the strong correlation between compound plasma levels, in vivo efficacy, and *in vitro* potency. The most potent compound, R921219, was active with circulating exposure levels of

approximately 10 μg/ml (68% inhibition at a dose level of 100 mg/kg) compared with R921302, a relatively less potent molecule, which reduced plasma extravasation by 42% at a dose level of 100 mg/kg. Further, the length of exposure to circulating compound was reflected in the duration of inhibitory activity. R921302, determined to be the most metabolically stable compound in pharmacokinetics studie, inhibited the vascular permeability for 1-2 hours prior to antigen-induced receptor signaling, where after the efficacy began to decrease. These data are summarized in TABLE 3 and TABLE 4.

TABLE 3

Efficacy of R921218, R926109, R921219 and R921302 in the PCA Assay

Compound	Route	Vehicle	Pretreatment time (min)	Dose (mg/kg)	% Inhibition	Plasma level (μg/ml)
R921218	PO	67%PEG/33% citrate buffer	10	50	7	3
				100	11	4
				200	50	18
R926109	PO	67%PEG/33% citrate buffer	15	50	22	N.D.
				100	32	
				200	48	
R921219	PO	1.5% Avicel/water	15	30	25	0.4
				100	68	4
				300	92	11
R921302	PO	1.5% Avicel/water	60	50	35	25
				100	42	38
				150	56	64
				200	93	105

TABLE 4

Duration of action of R921219 and R921302 in the PCA Assay

Compound	Route	Vehicle	Dose (mg/kg)	Pretreatment time (min)	% Inhibition	Plasma level (μg/ml)
RR921302	PO	1.5% Avicel/water	200	30	89	88
				60	83	53
				120	82	61
				240	37	8

Similar in vivo activity was observed with compounds R926495, R926508, R926742, R926745 and R926150, which were able to inhibit the PCA response after administration by the oral route in a PEG-based formulation (data not shown).

7.14 The Compounds Are Effective in the Treatment of Asthma

The efficacy of compounds R921218, R921302, R926495, R926508, R926742 and R921219 in the treatment of asthma was demonstrated in the sheep model of allergic asthma. Sheep develop bronchoconstriction within minutes of exposure to inhaled antigen (Ascaris suum), with maximal airflow obstruction during the early allergic response (EAR). Release of preformed mast cell mediators is likely responsible for this early phase of airflow obstruction. In addition to the EAR, the sheep model allows us to evaluate the effect of our compounds on the late asthmatic reaction (LAR) and non-specific airway hyperresponsiveness (AHR), which occur as a result of topical or local administration of allergen to the airway. In the sheep, AHR develops a few hours following antigen challenge, and can persist for up to 2 weeks. The results described below demonstrate the potential of the tested compounds to inhibit a cascade of events that may be a result of release of cytokines from the mast cell.

7.14.1 Study Protocol

In the sheep model of allergic asthma, sheep are administered aerosols of test article *via* an endotracheal tube, followed by an aerosol challenge with antigen extracted from the roundworm, Ascaris suum, to which the sheep are naturally allergic. Allergen challenge leads to direct bronchoconstriction (both EAR and LAR) and a persistent non-specific AHR. These three characteristics are similar to those seen in human allergic asthmatics. The activity of the test agent is determined by changes in the lung resistance (R_L), which is calculated from measurements of transpulmonary pressure, flow, and respiratory volume. The historical control data obtained from the same sheep following saline treatment compared with an allergen challenge show that a sharp increase of R_L occurs during the EAR and persists for approximately 2-3 hours following allergen challenge. The LAR is a less pronounced increase in R_L, which starts approximately 5-6 hours following allergen challenge and is resolved by 8 hours post-challenge. Twenty-four hours after the challenge, a dose response to carbachol is measured to determine the AHR, which is expressed as the dose of carbachol required to increase R_L by 400% over baseline. (This measurement is referred to as the provocative concentration of carbachol that elicits a 400% increase in RL over baseline (PC_{400}). The data are compared to historical control data for the same individual when administered a saline control aerosol and challenged with Ascaris suum.

7.14.2 Result

All the compounds tested showed inhibitory effects in the LAR and the AHR, and several of these agents inhibited the EAR as well. The optimal response for each compound in a series of studies to evaluate activity at several pretreatment times and using several different solution and suspension formulations are shown in TABLE 5. The efficacy of R921218 on the EAR appeared to be dependent on the formulation, with the greatest effect seen at 30 mg/sheep administered as a solution aerosol in 10% ethanol. R926495, R926742, R926508 and R921219, administered in four different sheep at 45 mg/sheep in an aqueous suspension 60 minutes prior to allergen challenge, demonstrate that the LAR and AHR is blocked. In addition to these late parameters, the EAR was greatly reduced by treatment with R921219, R926508 or R926495. The efficacy of RR921302 was investigated using a 45%PEG400/55% citrate buffer vehicle. Under these conditions, R921302, administered at 30 mg/sheep 60 minutes prior to challenge, blocked the LAR and AHR, and EAR was unaffected.

These data clearly demonstrate that these compounds are able to block the asthmatic responses in allergic sheep. All compounds inhibited the AHR and LAR significantly when compared to the historical control. The EAR was significantly inhibited by R921219, R926508 and R926495 (54%, 21% and 33% respectively). In contrast, R921218, R921302 and R926742 failed to inhibit the EAR when administered in an aqueous suspension.

TABLE 5

Efficacy Of Exemplary Compounds In A Sheep Model Of Allergic Asthma

Compound	Dose (mg/sheep)	Pretreatment time (min)	Vehicle	EAR (% inhibition)	LAR (% inhibition)	AHR (% inhibition)
R921218	30	15	10% ethanol	66	78	101
R926742	45	60	Aqueous suspension	-19	87	94
R926495	45	60		33	85	41
R926508	45	60		21	90	88
R921219	45	60		56	75	90
RR921302	30	60	45%PEG400/55% citrate buffer	-28	86	82

7.15 The Compounds Are Effective In The Treatment of Asthma

The efficacy of compounds R921304 and R921219 in the treatment of asthma was also demonstrated in a mouse model of allergic asthma.

7.15.1 Study protocol

Mice are sensitized to ovalbumin (chicken protein) in the presence of an adjuvant (Alum) by the intraperitoneal route on day 0 and day 7. One week later, mice are challenged intranasally with ovalbumin on Days 14, 15 and 16 (more stringent model) or on Day 14 (less stringent model). This sensitization and challenge regimen leads to airway hyperresponsiveness and inflammation in the lungs, which are two dominant characteristics of human allergic asthma. In the mouse model, the in vivo airway responses are measured using a whole body plethysmograph which determines the PENH (enhanced Pause, Buxco Electronics). The PENH is a dimensionless value comprised of the peak inspiratory flow (PIF), peak expiratory flow (PEF), time of inspiration, time of expiration and relaxation time, and is considered a validated parameter of airway responsiveness. Responses to allergen challenge (OVA) are compared with animals challenged with saline only. Twenty-four hours after challenge, mice are exposed to increasing doses of methacholine (muscarinic receptor agonist) which results in smooth muscle contraction. The ovalbumin-challenged mice demonstrate a significant airway hyperresponsiveness to methacholine when compared to the saline challenged mice. In addition, a cellular infiltrate in the airway is observed in ovalbumin challenged mice when compared with the saline challenged mice. This cellular infiltrate is mainly characterized by eosinophils, but a smaller influx of neutrophils and mononuclear cells is also present.

The use of this model for the evaluation of small molecule inhibitors of mast cell degranulation has been validated is several ways. First, using mast cell deficient mice (W/W^v) it has been shown that the ovalbumin-induced responses are dependent upon the presence of mast cells. In the mast cell deficient mice, ovalbumin sensitization and challenge did not result in airway hyperresponsiveness and eosinophil influx. Second, the mast cell stabilizer, Cromolyn, was able to block the ovalbumin-induced airway hyperresponsiveness and inflammation (data not shown). The use of this model to evaluate compounds for the treatment of asthmatic responses that may be mediated by mechanisms other than mast cell stablization, is further supported by the inhibitory effect of the steroids, dexamethasone and budesonide, on methacoline-induced bronchocontriction.

7.15.2 Results

The efficacy of R921304 was evaluated by intranasal administration on 10 consecutive days, from Day 7 through Day 16, at a dose level of 20 mg/kg, with the last 3 doses administered 30 minutes prior to either saline or ovalbumin challenge. R921304 was able to inhibit the ovalbumin-induced airway hyperresponsiveness to methacholine when compared to the vehicle treated mice.

In a less stringent protocol, in which the mice were challenged with ovalbumin only once on Day 14, R921219 administered subcutaneously at 70 mg/kg in 67%PEG400/33% citrate buffer 30 minutes prior to saline or ovalbumin challenge, demonstrates that R921219 completely blocked the ovalbumin-induced airway hyperresponsiveness and cellular influx.

These results clearly demonstrate that R921219 and R921304 are efficacious in inhibiting the airway responses in a mouse model of allergic asthma.

7.16 2,4-Pyrimidinediamine Compounds Inhibit Phosphorylation of Proteins Downstream of Syk kinase in Activated Mast Cells

The inhibitory effect of the 2,4-pyrimidinediamine compounds on the phosphorylation of proteins downstream of Syk kinase was tested with compounds R921218, R218219 and R921304 in IgE receptor-activiated BMMC cells.

For the assay, BMMC cells were incubated in the presence of varying concentrations of test compound (0.08 μM, 0.4 μM, 2 μM and 10 μM) for 1 hr at 37°C. The cells were then stimulated with anti-IgE antibody as previously described. After 10 min, the cells were lysed and the cellular proteins separated by electrophoresis (SDS PAGE).

Following electrophoresis, the phosphorylation of the proteins indicated in FIGS. 7, 10 and 11A-D were assessed by immunoblot. Antibodies were purchased from Cell Signaling Technology, Beverley, MA.

Referring to FIGS. 7, 10 and 11A-D, the indicated compounds tested inhibited phosphorylation of proteins downstream of Syk, but not upstream of Syk, in the IgE receptor signaling cascade, confirming both that the compounds inhibit upstream IgE induced degranulation, and that the compounds exhert their inhibitory activity by inhibiting Syk kinase.

7.17 2,4-Pyrimidinediamine Compounds Inhibit Syk Kinase in Biochemical Assays

Several 2,4-pyrimidinediamine compounds were tested for the ability to inhibit Syk kinase catalyzed phosphorylation of a peptide substrate in a biochemical fluorescenced polarization assay with isolated Syk kinase. In this experiment, Compounds were diluted to 1% DMSO in kinase buffer (20 mM HEPES, pH 7.4, 5 mM $MgCl_2$, 2 mM $MnCl_2$, 1 mM DTT, 0.1 mg/mL acetylated Bovine Gamma Globulin). Compound in 1% DMSO (0.2% DMSO final) was mixed with ATP/substrate solution at room temperature. Syk kinase (Upstate, Lake Placid NY) was added to a final reaction volume of 20 uL, and the reaction was incubated for 30 minutes at room temperature. Final enzyme reaction conditions were 20 mM HEPES, pH 7.4, 5 mM $MgCl_2$, 2 mM $MnCl_2$, 1 mM DTT, 0.1 mg/mL acetylated Bovine Gamma Globulin, 0.125 ng Syk, 4 uM ATP, 2.5 uM peptide substrate (biotin-EQEDEPEGDYEEVLE-CONH2, SynPep Corporation). EDTA (10 mM final)/anti-phosphotyrosine antibody (1X final)/fluorescent phosphopeptide tracer (0.5X final) was added in FP Dilution Buffer to stop the reaction for a total volume of 40 uL according to manufacturer's instructions (PanVera Corporation) The plate was incubated for 30 minutes in the dark at room temperature. Plates were read on a Polarion fluorescence polarization plate reader (Tecan). Data were converted to amount of phosphopeptide present using a calibration curve generated by competition with the phosphopeptide competitor provided in the Tyrosine Kinase Assay Kit, Green (PanVera Corporation).

The results of the assay are shown in TABLE 6, below:

TABLE 6

Compound No.	IC50 (in μM)
R926505	0.0703
R926508	0.1315
R926594	0.7705
R926715	0.534
R926745	0.0925
R926782	0.1165
R926791	0.207
R926813	0.4047
R926816	0.0615
R935138	0.2288
R935190	0.0465

TABLE 6	
Compound No.	IC50 (in μM)
R935191	0.045
R935193	0.075
R935194	0.1687
R935196	0.2655
R940255	0.7705
R940256	2.787
R940269	0.685
R940275	0.7335
R940276	0.1265
R940277	0.2143
R940290	0.187
R945071	0.4295
R945140	0.611
R945142	2.007
R945144	0.383
R921302	0.2678
R908702	0.0378
R908712	0.024
R909268	0.1253
R920410	0.157
R926753	0.108
R926757	0.5103
R926834	0.292
R926839	0.055
R926891	0.1695
R926931	0.2553
R935237	0.0455
R935293	0.0465
R935302	0.0265
R935304	0.042
R935307	0.057
R935309	0.098
R935310	0.2003
R940323	0.062
R940338	0.028

TABLE 6	
Compound No.	**IC50 (in μM)**
R921303	0.00045
R940347	0.0345
R921304	0.01275
R950368	0.0107
R950373	0.0665

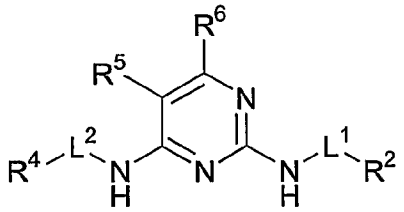
These data demonstrate that all of the compounds tested, except for R945142 and R909236 inhibit Syk kinase phosphorylation with IC_{50}s in the submicromolar range. All compounds tested inhibit Syk kinase phosphorylation with IC_{50}s in the micromolar range.

Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

All literature and patent references cited throughout the application are incorporated by reference into the application for all purposes.

What is Claimed Is:

1. A compound according to structural formula (I):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond and a linker;

R^2 is selected from the group consisting of (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^4 is selected from the group consisting of hydrogen, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^5 is selected from the group consisting of R^6, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C1-C4) alkanyl optionally substituted with one

or more of the same or different R^8 groups, (C2-C4) alkenyl optionally substituted with one or more of the same or different R^8 groups and (C2-C4) alkynyl optionally substituted with one or more of the same or different R^8 groups;

each R^6 is independently selected from the group consisting of hydrogen, an electronegative group, $-OR^d$, $-SR^d$, (C1-C3) haloalkyloxy, (C1-C3) perhaloalkyloxy, $-NR^cR^c$, halogen, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$; $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-OC(O)R^d$, $-SC(O)R^d$, $-OC(O)OR^d$, $-SC(O)OR^d$, $-OC(O)NR^cR^c$, $-SC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-SC(NH)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$ and $-[NHC(NH)]_nNR^cR^c$, (C5-C10) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups, (C6-C16) arylalkyl optionally substituted with one or more of the same or different R^8 groups, 5-10 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups and 6-16 membered heteroarylalkyl optionally substituted with one or more of the same or different R^8 groups;

R^8 is selected from the group consisting of R^a, R^b, R^a substituted with one or more of the same or different R^a or R^b, $-OR^a$ substituted with one or more of the same or different R^a or R^b, $-B(OR^a)_2$, $-B(NR^cR^c)_2$, $-(CH_2)_m-R^b$, $-(CHR^a)_m-R^b$, $-O-(CH_2)_m-R^b$, $-S-(CH_2)_m-R^b$, $-O-CHR^aR^b$, $-O-CR^a(R^b)_2$, $-O-(CHR^a)_m-R^b$, $-O-(CH_2)_m-CH[(CH_2)_mR^b]R^b$, $-S-(CHR^a)_m-R^b$, $-C(O)NH-(CH_2)_m-R^b$, $-C(O)NH-(CHR^a)_m-R^b$, $-O-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-S-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-O-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-S-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-NH-(CH_2)_m-R^b$, $-NH-(CHR^a)_m-R^b$, $-NH[(CH_2)_mR^b]$, $-N[(CH_2)_mR^b]_2$, $-NH-C(O)-NH-(CH_2)_m-R^b$, $-NH-C(O)-(CH_2)_m-CHR^bR^b$ and $-NH-(CH_2)_m-C(O)-NH-(CH_2)_m-R^b$;

each R^a is independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C5-C10) aryl, phenyl, (C6-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, morpholinyl, piperazinyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from the group consisting of =O, $-OR^d$, (C1-C3) haloalkyloxy, $-OCF_3$, =S, $-SR^d$, $=NR^d$, $=NOR^d$, $-NR^cR^c$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-C(NR^a)NR^cR^c$, $-C(NOH)R^a$, $-C(NOH)NR^cR^c$, $-OC(O)R^d$, $-OC(O)OR^d$, $-OC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-OC(NR^a)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NR^aC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NR^aC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$, $-[NR^aC(O)]_nNR^cR^c$, $-[NHC(NH)]_nNR^cR^c$ and $-[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is independently a protecting group or R^a, or, alternatively, each R^c is taken together with the nitrogen atom to which it is bonded to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which may optionally be substituted with one or more of the same or different R^a or suitable R^b groups;

each R^d is independently a protecting group or R^a;

each *m* is independently an integer from 1 to 3; and

each *n* is independently an integer from 0 to 3,

with the provisos that:

(1) when L^1 is a direct bond and R^6 is hydrogen, then R^2 is not 3,4,5-tri (C1-C6) alkoxyphenyl;

(2) when L^1 and L^2 are each a direct bond, R^2 is a substituted phenyl and R^6 is hydrogen, then R^5 is other than cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl;

(3) when L^1 and L^2 are each a direct bond and R^2 and R^4 are each independently a substituted or unsubstituted pyrrole or indole, then the R^2 and R^4 are attached to the remainder of the molecule *via* a ring carbon atom; and

(4) the compound is not

N2,N4-bis(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R070790);

N2,N4-bis(2-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R081166);

N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R088814);

N2,N4-bis(2-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R088815);

N2,N4-bisphenyl-5-fluoro-2,4-pyrimidinediamine (R091880);

N2,N4-bis(3-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R092788);

N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R067962);

N2,N4-bis(2,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067963);

N2,N4-bis(3,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067964);

N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R070153);

N2,N4-bis(2,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R070791);

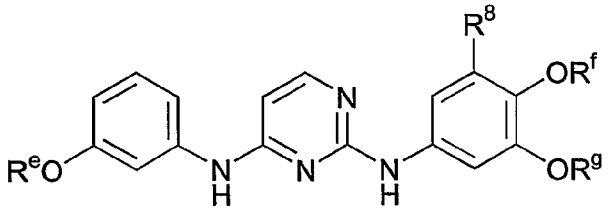
N2,N4-bis(3-bromophenyl)-5-fluoro-2,4-pyrimidinediamine (R008958);

N2,N4-bis(phenyl)-5-fluoro-2,4-pyrimidinediamine;

N2,N4-bis(morpholino)-5-fluoro-2,4-pyrimidinediamine;

N2,N4-bis[(3-chloro-4-methoxyphenyl)]-5-fluoro-2,4-pyrimidinediamine; N2-(3,4,5-trimethoxyphenyl)-N4-(3,5-dimethoxyphenyl)-2,4-pyrimidinediamine; N2-(3,4-dimethoxyphenyl)-N4-(3-methoxyphenyl)-2,4-pyrimidinediamine; N2,N4-bis(3,4-dimethoxyphenyl)-2,4-pyrimidinediamine; N2,N4-Bis(3-chloro-4-methoxy-5-fluoro-2,4-pyrimidinediamine; N2-[4-(3-dimethylamino-2-hydroxy-propyloxy)phenyl]-N4-3,4-dichlorophenyl-5-chloro-2,4-pyrimidinediamine; N2-[4-(3-dimethylamino-2-hydroxy-propyloxy)phenyl]-N4-3,4-dichlorophenyl-2,4-pyrimidinediamine; N2-[4-(3-dimethylamino-2-hydroxy-propyloxy)phenyl]-N4-3,4-dichlorophenyl-5-methyl-2,4-pyrimidinediamine; N2-(4-benzoxyphenyl)-N4-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine; N2,N4-bis(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine; N2,N4-bis(3,4,5-trimethoxyphenyl)-5-bromo-2,4-pyrimidinediamine; N2-(1-benzyl-1H-indazol-5-yl)-N4-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine; N2-(1H-indol-1-yl)-N4-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-aminosulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[2-methoxy-5-(5-methyl-3-isoxazoly-methylsulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-methyl aminosulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-ethylsulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-isobutylsulfonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-[(2-methoxy-5-propylcarbonyl)phenyl]-N4-(3-methyl-1H-indazol-6-yl)-2,4-pyrimidinediamine; N2-(1H-indazol-5-yl)-N4-propynyl-5-bromo-2,4-pyrimidinediamine; N2-(1-H-indol-5-yl)-N4-[1-(3-methyl-1-hydroxy)butyl]-N4-(1H-indol-5-yl)-5-bromo-2,4-pyrimidinediamine; N2-(1-dimethylaminosulfonyl-1H-indol-5-yl)-N4-[1-(2-

methyl-2-hydroxy)ethyl]-5-bromo-2,4-pyrimidinediamine, or a compound according to the formula:



wherein: R^e is (C1-C6) alkyl; R^f and R^g are each, independently of one another, a straight-chain or branched (C1-C6) alkyl which is optionally substituted with one or more of the same or different R^8 groups; and R^8 is as defined above.

2. The compound of Claim 1 in which L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond, (C1-C3) alkyldiyl optionally substituted with one or more of the same or different R^9 groups and 1-3 membered heteroalkyldiyl optionally substituted with one or more of the same or different R^9 groups, wherein:

R^9 is selected from the group consisting of (C1-C3) alkyl, $-OR^a$, $-C(O)OR^a$, (C5-C10) aryl optionally substituted with one or more of the same or different halogens, phenyl optionally substituted with one or more of the same or different halogens, 5-10 membered heteroaryl optionally substituted with one or more of the same or different halogens and 6 membered heteroaryl optionally substituted with one or more of the same or different halogens; and

R^a is as defined in Claim 1.

3. The compound of Claim 2 in which L^1 and L^2 are each, independently of one another, selected from the group consisting of methano, ethano and propano, each of which may be optionally monosubstituted with an R^9 group.

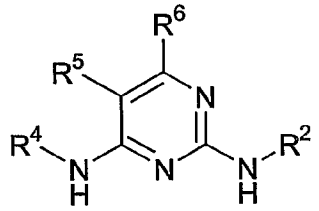
4. The compound of Claim 3 in which the R^9 group is selected from the group consisting of $-OR^a$, $-C(O)OR^a$, halophenyl and 4-halophenyl, wherein R^a is as defined in Claim 1.

5. The compound of Claim 1 in which R^6 is hydrogen.

6. The compound of Claim 1 or 5 in which R^5 is selected from the group consisting of an electronegative group, halo, -F, -CN, $-NO_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)CF_3$, $-C(O)OCF_3$, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl (C1-C3) haloalkoxy, (C1-C3) perhaloalkoxy, $-OCF_3$ and $-CF_3$.

7. The compound of Claim 1 in which at least one of L1 or L2 is a direct bond.

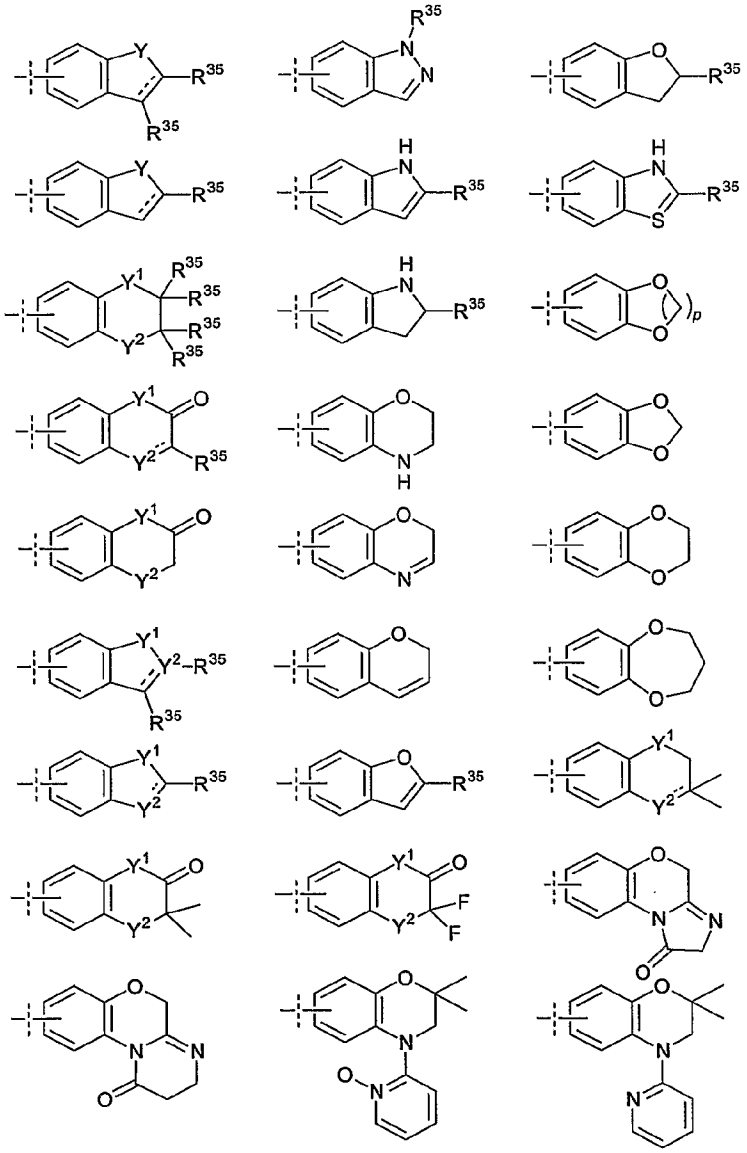
8. The compound of Claim 1 according to the structure (Ia):

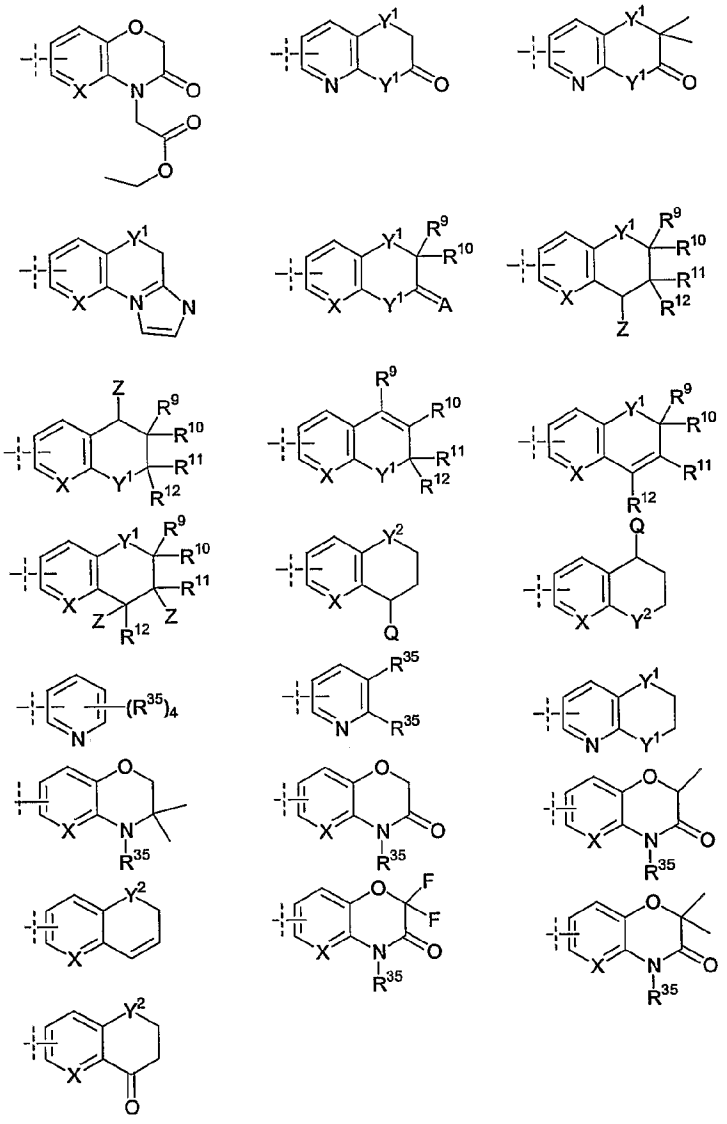


and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein R^2, R^4, R^5 and R^6 are as defined in Claim 1.

9. The compound of Claim 8 in which R^2 is selected from the group consisting of phenyl, naphthyl, 5-10 membered heteroaryl, benzodioxanyl, 1,4-benzodioxan-(5 or 6)-yl, benzodioxolyl, 1,3-benzodioxol-(4 or 5)-yl, benzoxazinyl, 1,4-benzoxazin-(5,6,7 or 8)-yl, benzoxazolyl, 1,3-benzoxazol-(4,5,6 or 7)-yl, benzopyranyl, benzopyran-(5,6,7 or 8)-yl, benzotriazolyl, benzotrazol-(4,5,6 or 7)-yl, 1,4-benzoxazinyl-2-one, 1,4-benzoxazin-(5,6,7 or 8)-yl-2-one, 2H-1,4-benzoxazinyl-3(4H)-one, 2H-1,4-benzoxazin-(5,6,7 or 8)-yl-3(4H)-one, 2H-1,3-benzoxazinyl-2,4(3H)-dione, 2H-1,3-benzoxazin-(5,6,7 or 8)-yl-2,4(3H)-dione, benzoxazolyl-2-one, benzoxazol-(4,5,6 or 7)-yl-2-one, dihydrocoumarinyl, dihydrocoumarin-(5,6,7 or 8)-yl, 1,2-benzopyronyl, 1,2-benzopyron-(5,6,7 or 8)-yl, benzofuranyl, benzofuran-(4,5,6 or 7)-yl, benzo[b]furanyl, benzo[b]furan-(4,5,6 or 7)-yl, indolyl, indol-(4,5,6 or 7)-yl, pyrrolyl and pyrrol-(1 or 2)-yl, each of which may be optionally substituted with one or more of the same or different R^8 groups, where R^8 is as defined in Claim 1.

10. The compound of Claim 8 in which R^2 and/or R^4 are each, independently of one another, a heteroaryl selected from the group consisting of:





wherein:

p is an integer from one to three;

each - - - independently represents a single bond or a double bond;

R^{35} is hydrogen or R^8, where R^8 is as previously defined for structural formula (I);

X is selected from the group consisting of CH, N and N-O;

each Y is independently selected from the group consisting of O, S and NH;

each Y^1 is independently selected from the group consisting of O, S, SO, SO_2, $SONR^{36}$, NH and NR^{37};

each Y^2 is independently selected from the group consisting of CH, CH_2, O, S, N, NH and NR^{37};

R^{36} is hydrogen or alkyl;

R^{37} is selected from the group consisting of hydrogen and a progroup, preferably hydrogen or a progroup selected from the group consisting of aryl, arylalkyl, heteroaryl, R^a, R^b–CR^aR^b-O-C(O)R^8, -CR^aR^b-O-$PO(OR^8)_2$, -CH_2-O-$PO(OR^8)_2$, -CH_2-$PO(OR^8)_2$, -C(O)-CR^aR^b-$N(CH_3)_2$, -CR^aR^b-O-C(O)-CR^aR^b-$N(CH_3)_2$, -C(O)R^8, -$C(O)CF_3$ and –C(O)-NR^8-C(O)R^8;

R^{38} is selected from the group consisting of alkyl and aryl;

A is selected from the group consisting of O, NH and NR^{38};

R^9, R^{10}, R^{11} and R^{12} are each, independently of one another, selected from the group consisting of alkyl, alkoxy, halogen, haloalkoxy, aminoalkyl and hydroxyalkyl, or, alternatively, $R^9$and R^{10} and/or R^{11} and R^{12} are taken together form a ketal;

each Z is selected from the group consisting of hydroxyl, alkoxy, aryloxy, ester, carbamate and sulfonyl;

Q is selected from the group consisting of –OH, OR^8, $–NR^cR^c$, -NHR^{39}-C(O)R^8, -NHR^{39}-C(O)OR^8, -NR^{39}-CHR^{40}-R^b, -NR^{39}-$(CH_2)_m$-R^b and –NR^{39}-C(O)-CHR^{40}-NR^cR^c;

R^{39} and R^{40} are each, independently of one another, selected from the group consisting of hydrogen, alkyl, aryl, alkylaryl;arylalkyl and NHR^8; and

R^a, R^b and R^c are as previously defined for structural formula (I).

11. The compound of Claim 10 in which R^2 and R^4 are the same.

12. The compound of Claim 10 or 11 in which each R^{35} is independently selected from the group consisting of hydrogen, R^d, -NR^cR^c, -$(CH_2)_m$-NR^cR^c, -C(O)NR^cR^c, -$(CH_2)_m$-C(O)NR^cR^c, -C(O)OR^d, -$(CH_2)_m$-C(O)OR^d and –$(CH_2)_m$-OR^d, where *m*, R^c and R^d are as defined in Claim 1.

13. The compound of Claim 12 in which each *m* is one.

14. The compound of Claim 8 in which R^2 is an optionally substituted heteroaryl which is attached to the remainder of the molecule *via* a ring carbon atom.

15. The compound of Claim 8 in which R^4 is an optionally substituted heteroaryl which is attached to the remainder of the molecule *via* a ring carbon atom.

16. The compound of Claim 8 in which R^2 and/or R^4 are each, independently of one another, a phenyl optinally substituted with one, two or three R^8 groups, where R^8 is as defined in Claim 1.

17. The compound of Claim 16 in which R^2 and R^4 are each the same or different optionally substituted phenyl.

18. The compound of Claim 16 or 17 in which the optionally substituted phenyl is *mono* substituted.

19. The compound of Claim 18 in which the R^8 substituent is at the *ortho, meta* or *para* position.

20. The compound of Claim 19 in which R^8 is selected from the group consisting of (C1-C10) alkyl, (C1-C10) branched alkyl, $-OR^d$, $-O-(CH_2)_m-NR^cR^c$, $-O-C(O)NR^cR^c$, $-O-(CH_2)_m-C(O)NR^cR^c$, $-O-C(O)OR^a$, $-O-(CH_2)_m-C(O)OR^a$, $-O-C(NH)NR^cR^c$, $-O-(CH_2)_m-C(NH)NR^cR^c$, $-NH-(CH_2)_m-NR^cR^c$, $-NH-C(O)NR^cR^c$ and $-NH-(CH_2)_m-C(O)NR^cR^c$, where *m*, R^a, R^c and R^d are as defined in Claim 1.

21. The compound of Claim 16 or 17 in which the optionally substituted phenyl is a disubstituted phenyl.

22. The compound of Claim 21 in which the R^8 substituents are positioned 2,3-; 2,4-; 2,5-; 2,6-; 3,4-; or 3,5-.

23. The compound of Claim 21 in which each R^8 is independently selected from the group consisting of (C1-C10) alkyl, (C1-C10) branched alkyl, $-OR^a$ optionally substituted with

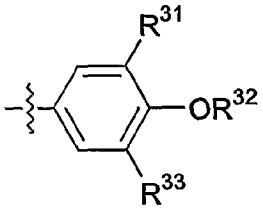
one or more of the same or different R^a or R^b groups, -O-$(CH_2)_m$-NR^cR^c, –O-C(O)NR^cR^c, -O-$(CH_2)_m$-C(O)NR^cR^c, -O-C(O)OR^a, -O-$(CH_2)_m$-C(O)OR^a, -O-C(NH)NR^cR^c, -O-$(CH_2)_m$-C(NH)NR^cR^c, -NH-$(CH_2)_m$-NR^cR^c, -NH-C(O)NR^cR^c and -NH-$(CH_2)_m$-C(O)NR^cR^c, where *m*, R^a, R^b and R^c are as defined in Claim 1.

24. The compound of Claim 16 or 17 in which the optionally substituted phenyl is trisubstituted.

25. The compound of Claim 24 in which the R^8 substituents are positioned 2,3,4; 2,3,5; 2,3,6; 2,4,5; 2,4,6; 2,5,6; or 3,4,5.

26. The compound of Claim 25 which each R^8 is independently selected from the group consisting of (C1-C10) alkyl, (C1-C10) branched alkyl, -OR^a optionally substituted with one or more of the same or different R^a or R^b groups, -O-$(CH_2)_m$-NR^cR^c, –O-C(O)NR^cR^c, -O-$(CH_2)_m$-C(O)NR^cR^c, -O-C(O)OR^a, -O-C(NH)NR^cR^c, -O-$(CH_2)_m$-C(O)OR^a, -O-$(CH_2)_m$–C(NH)NR^cR^c, -NH-$(CH_2)_m$-NR^cR^c, -NH-C(O)NR^cR^c and -NH-$(CH_2)_m$-C(O)NR^cR^c, where *m*, R^a, R^b and R^c are as defined in Claim 1.

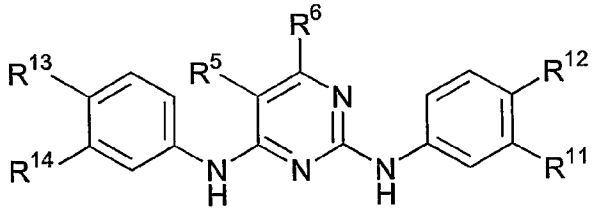
27. The compound of Claim 24 in which the trisubstituted phenyl has the formula:



wherein: R^{31} is methyl or (C1-C6) alkyl; R^{32} is hydrogen, methyl or (C1-C6) alkyl; and R^{33} is a halo group.

28. The compound of Claim 17 in which R^2 and R^4 are the same.

29. The compound of Claim 8 according to structural formula (Ib):

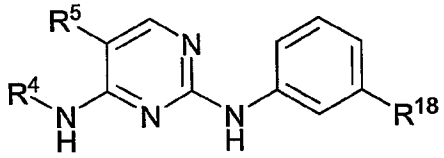


and salts, hydrates, solvates and N-oxides thereof, wherein R^{11}, R^{12}, R^{13} and R^{14} are each, independently of one another, selected from the group consisting of hydrogen, hydroxy, (C1-C6) alkoxy and $-NR^cR^c$; and R^5, R^6 and R^c are as defined in Claim 1.

30. The compound of Claim 29 in which R^{11}, R^{12}, R^{13} and R^{14} are each hydrogen.

31. The compound of Claim 29 in which R^{12} and R^{13} are each hydrogen.

32. The compound of Claim 8 according to structural formula (Ic):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

R^4 is phenyl optionally substituted with from 1 to 3 of the same or different R^8 groups or 5-14 membered heteroaryl optionally substituted with from 1 to 4 of the same or different R^8 groups;

R^5 is an electronegative group, F or CF_3; and

R^{18} is $-O(CH_2)_m-R^b$, where m and R^b are as defined in Claim 1.

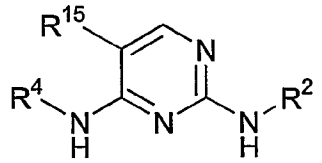
33. The compound of Claim 32 in which R^4 is an optionally substituted heteroaryl.

34. The compound of Claim 32 in which R^{18} is -O-CH_2-C(O)-$NHCH_3$.

35. The compound of Claim 1 which inhibits mast cell or basophil cell degranulation as measured in an *in vitro* assay.

36. The compound of Claim 35 which has an IC50 of about 20 μM or less.

37. A compound according to structural formula (Id):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

R^2 and R^4 are as defined in Claim 1; and

R^{15} is an electronegative group,

with the provisos that:

(1) when R^2 is 3,4,5-tri (C1-C6) alkoxyphenyl and R^{15} is halogen, then R^4 is not 3,4,5-tri (C1-C6) alkoxyphenyl;

(2) when R^2 is a substituted phenyl group, then R^{15} is other than cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl; and

(3) the compound is not

N2,N4-bis(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R070790);

N2,N4-bis(2-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R081166);

N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R088814);

N2,N4-bis(2-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R088815);

N2,N4-bisphenyl-5-fluoro-2,4-pyrimidinediamine (R091880);

N2,N4-bis(3-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R092788);

N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R067962);

N2,N4-bis(2,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067963);

N2,N4-bis(3,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067964);

N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R0707153);
N2,N4-bis(2,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R070791);
N2,N4-bis(3-bromophenyl)-5-fluoro-2,4-pyrimidinediamine (R008958);
N2,N4-bis(phenyl)-5-fluoro-2,4-pyrimidinediamine;
N2,N4-bis(morpholino)-5-fluoro-2,4-pyrimidinediamine; or
N2,N4-bis[(3-chloro-4-methoxyphenyl)]-5-fluoro-2,4-pyrimidinediamine.

38. The compound of Claim 37 in which when R^{15} is halogen or nitro, then R^2 is not 3,4,5-tri (C1-C6) alkoxyphenyl.

39. The compound of Claim 38 in which R^{15} is selected from the group consisting of –CN, -NC, $-NO_2$, halogen, -F, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, (C1-C3) fluoroalkyl, (C1-C3) perfluoroalkyl, $-CF_3$, (C1-C3) haloalkoxy, (C1-C3) perhaloalkoxy, (C1-C3) fluoroalkoxy, (C1-C3) perfluoroalkoxy and $-OCF_3$.

40. The compound of Claim 39 in which R^{15} is selected from the group consisting of halo, Br, F, $-CF_3$ and $-NO_2$.

41. The compound of Claim 37 which inhibits mast cell or basophil cell degranulation as measured in an *in vitro* assay.

42. The compound of Claim 41 which has an IC_{50} of about 20 μM or less.

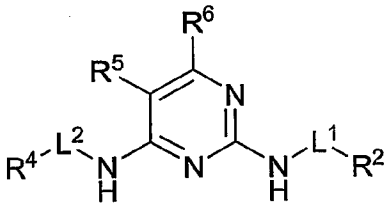
43. A compound selected from any compound in TABLE 1 which inhibits mast cell or basophil cell degranulation as measured in an *in vitro* assay, with the proviso that the compound is not

N2,N4-bis(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R070790);
N2,N4-bis(2-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R081166);
N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R088814);
N2,N4-bis(2-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R088815);
N2,N4-bisphenyl-5-fluoro-2,4-pyrimidinediamine (R091880);

N2,N4-bis(3-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R092788);
N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R067962);
N2,N4-bis(2,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067963);
N2,N4-bis(3,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067964);
N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R070153);
N2,N4-bis(2,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R070791); or
N2,N4-bis(3-bromophenyl)-5-fluoro-2,4-pyrimidinediamine (R008958).

44. The compound of Claim 43 which has an IC_{50} of about 20 μM or less.

45. A pharmaceutical composition comprising a pyrimidinediamine compound and a pharmaceutically acceptable excipient, carrier or dilutent, said pyrimidinediamine compound being a compound according to structural formula (I):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond and a linker;

R^2 is selected from the group consisting of (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more

of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^4 is selected from the group consisting of hydrogen, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^5 is selected from the group consisting of R^6, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C1-C4) alkanyl optionally substituted with one or more of the same or different R^8 groups, (C2-C4) alkenyl optionally substituted with one or more of the same or different R^8 groups and (C2-C4) alkynyl optionally substituted with one or more of the same or different R^8 groups;

each R^6 is independently selected from the group consisting of hydrogen, an electronegative group, $-OR^d$, $-SR^d$, (C1-C3) haloalkyloxy, (C1-C3) perhaloalkyloxy, $-NR^cR^c$, halogen, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$; $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-OC(O)R^d$, $-SC(O)R^d$, $-OC(O)OR^d$, $-SC(O)OR^d$, $-OC(O)NR^cR^c$, $-SC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-SC(NH)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$ and $-[NHC(NH)]_nNR^cR^c$, (C5-C10) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups, (C6-C16) arylalkyl optionally substituted with one or more of the same or different R^8 groups, 5-10 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups and 6-16 membered heteroarylalkyl optionally substituted with one or more of the same or different R^8 groups;

R^8 is selected from the group consisting of R^a, R^b, R^a substituted with one or more of the same or different R^a or R^b, $-OR^a$ substituted with one or more of the same or different R^a or

R^b, $-B(OR^a)_2$, $-B(NR^cR^c)_2$, $-(CH_2)_m-R^b$, $-(CHR^a)_m-R^b$, $-O-(CH_2)_m-R^b$, $-S-(CH_2)_m-R^b$, $-O-CHR^aR^b$, $-O-CR^a(R^b)_2$, $-O-(CHR^a)_m-R^b$, $-O-(CH_2)_m-CH[(CH_2)_mR^b]R^b$, $-S-(CHR^a)_m-R^b$, $-C(O)NH-(CH_2)_m-R^b$, $-C(O)NH-(CHR^a)_m-R^b$, $-O-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-S-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-O-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-S-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-NH-(CH_2)_m-R^b$, $-NH-(CHR^a)_m-R^b$, $-NH[(CH_2)_mR^b]$, $-N[(CH_2)_mR^b]_2$, $-NH-C(O)-NH-(CH_2)_m-R^b$, $-NH-C(O)-(CH_2)_m-CHR^bR^b$ and $-NH-(CH_2)_m-C(O)-NH-(CH_2)_m-R^b$;

each R^a is independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C5-C10) aryl, phenyl, (C6-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, morpholinyl, piperazinyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from the group consisting of =O, $-OR^d$, (C1-C3) haloalkyloxy, $-OCF_3$, =S, $-SR^d$, $=NR^d$, $=NOR^d$, $-NR^cR^c$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-C(NR^a)NR^cR^c$, $-C(NOH)R^a$, $-C(NOH)NR^cR^c$, $-OC(O)R^d$, $-OC(O)OR^d$, $-OC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-OC(NR^a)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NR^aC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NR^aC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$, $-[NR^aC(O)]_nNR^cR^c$, $-[NHC(NH)]_nNR^cR^c$ and $-[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is independently R^a or, alternatively, each R^c is taken together with the nitrogen atom to which it is bonded to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which may optionally be substituted with one or more of the same or different R^a or suitable R^b groups;

each R^d is independently R^a;

each *m* is independently an integer from 1 to 3; and

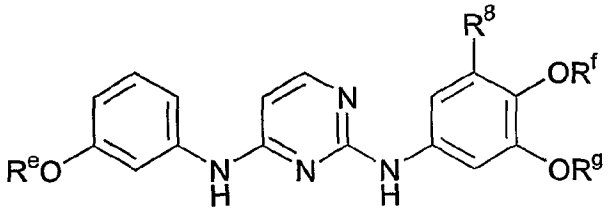
each *n* is independently an integer from 0 to 3, with the provisos that:

(1) when L^1 is a direct bond and R^6 is hydrogen, then R^2 is not 3,4,5-tri (C1-C6) alkoxyphenyl;

(2) when L^1 and L^2 are each direct bonds, R^2 is a substituted phenyl and R^6 is hydrogen, then R^5 is other than cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl;

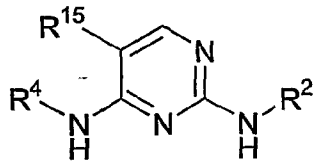
(3) when R^2 and R^4 are each independently a substituted or unsubstituted pyrrole or indole, then R^2 and R^4 are attached to the remainder of the molecule *via* a ring carbon atom; and

(4) the compound is not:



wherein: R^e is (C1-C6) alkyl; R^f and R^g are each, independently of one another a straight-chain or branched (C1-C6) alkyl which is optionally substituted with one or more of the same or different R^8 groups; and R^8 is as defined above.

46. A pharmaceutical composition comprising a pyrimidinediamine compound and a pharmaceutically acceptable carrier, diluent or excipient, said pyrimidinediamine compound being a compound according to structural formula (Id):



and salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

R^2 and R^4 are as defined for Claim 1; and

R^{15} is an electronegative group, with the provisos that:

(1) when R^2 is 3,4,5-tri (C1-C6) alkoxyphenyl and R^{15} is halogen, then R^4 is not 3,4,5-tri (C1-C6) alkoxyphenyl; and

(2) when R^2 is a substituted phenyl, then R^{15} is other than cyano or -C(O)NHR, where R is hydrogen or (C1-C6) alkyl.

47. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.

48. A pharmaceutical composition comprising a compound selected from any compound in TABLE 1 which inhibits mast cell or basophil cell degranulation as measured in an *in vitro* assay and a pharmaceutically acceptable carrier, diluent or excipient.

49. The composition of any one of Claims 46-48 in which the compound is in the form of a pharmaceutically acceptable salt.

50. The composition of Claim 49 in which the salt is a hydrochloride salt, a hydrogen sulfate salt, a sulfate salt, a phosphate salt, an alkane sulfonate salt, a methane sulfonate salt, an ethane sulfonate salt or a *p*-tolune sulfonate salt.

51. A method of inhibiting cell degranulation, comprising contacting a cell with an amount of a compound according to any one of Claims 1, 37 or 43 effect to inhibit degranulation.

52. The method of Claim 51 in which the cell is a human mast, basophil cell, neutrophil or eosinophil cell.

53. A method of inhibiting cell degranulation, comprising contacting a mast or basophil cell with an amount of a composition according to any one of Claims 46-48 effective to inhibit degranulation.

54. The method of Claim 53 in which the cell is a human mast, basophil cell, neutrophil or eosinophil cell.

55. A method of treating a disease characterized by, caused by or associated with mast or basophil cell degranulation, comprising administering to an animal suffering from such a disease an effective amount of a composition according to any one of Claims 46-48.

56. The method of Claim 55 in which the animal is a human.

57. The method of Claim 55 in which the disease is selected from the group consisting of allergic diseases, low grade scarring, diseases associated with tissue destruction, diseases associated with tissue inflammation, inflammation, and scarring.

58. The method of Claim 57 in which the allergic disease is selected from the group consisting of conjunctivitis, rhinitis, asthma, atopic dermatitis and food allergies.

59. The method of Claim 57 in which the low grade scarring is selected from the group consisting of scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury and post myocardial infarction.

60. The method of Claim 57 in which the disease associated with tissue destruction is selected form the group consisting of COPD, cardiobronchitis and post myocardial infarction.

61. The method of Claim 57 in which the disease associated with tissue inflammation is selected from the group consisting of irritable bowel, spastic colon and inflammatory colon disease.

62. A method of inhibiting a Syk kinase, comprising the step of contacting the Syk kinase or an active fragment thereof with an effective amount of a 2,4-pyrimidinediamine compound according to Claim 1.

63. The method of Claim 62 which is practiced *in vitro* with an isolated or recombinant Syk kinase.

64. The method of Claim 62 in which the Syk kinase is practiced *in vitro* with a cell or cell population that expresses an endogenous or recombinant Syk kinase.

65. The method of Claim 62 which is practiced *in vivo*.

66. A method of inhibiting a Syk kinase in an animal, comprising the step of administering to the animal an amount of a 2,4-pyrimidinediamine compound according to Claim 1 effective to inhibit the Syk kinase.

67. A method of treating or preventing a disease mediated at least in part by Syk kinase activity, comprising the step of administering to an animal in need thereof an amount of a 2,4-pyrimidinediamine compound according to Claim 1 effective to inhibit the Syk kinase activity, thereby treating or preventing the disease.

68. A method of treating or preventing a disease mediated at least in part by Syk kinase activity, comprising the step of administering to an animal in need thereof an amount of a composition according to Claim 46 effective to inhibit the Syk kinase activity, thereby treating or preventing the disease.

69. The method of Claim 72 or 74 in which the animal is a human.

70. A method of inhibiting an Fc receptor signal transduction cascade, contacting a cell comprising an Fc receptor having a gamma homodimer with an amount of a 2,4-pyrimidinediamine compound according to Claim 1 effective to inhibit its signal transduction cascade.

71. The method of Claim 70 in which the Fc receptor is selected from the group consisting of FcαRI, FCγRI, FCγRIII and FcεRI.

FIG. 1

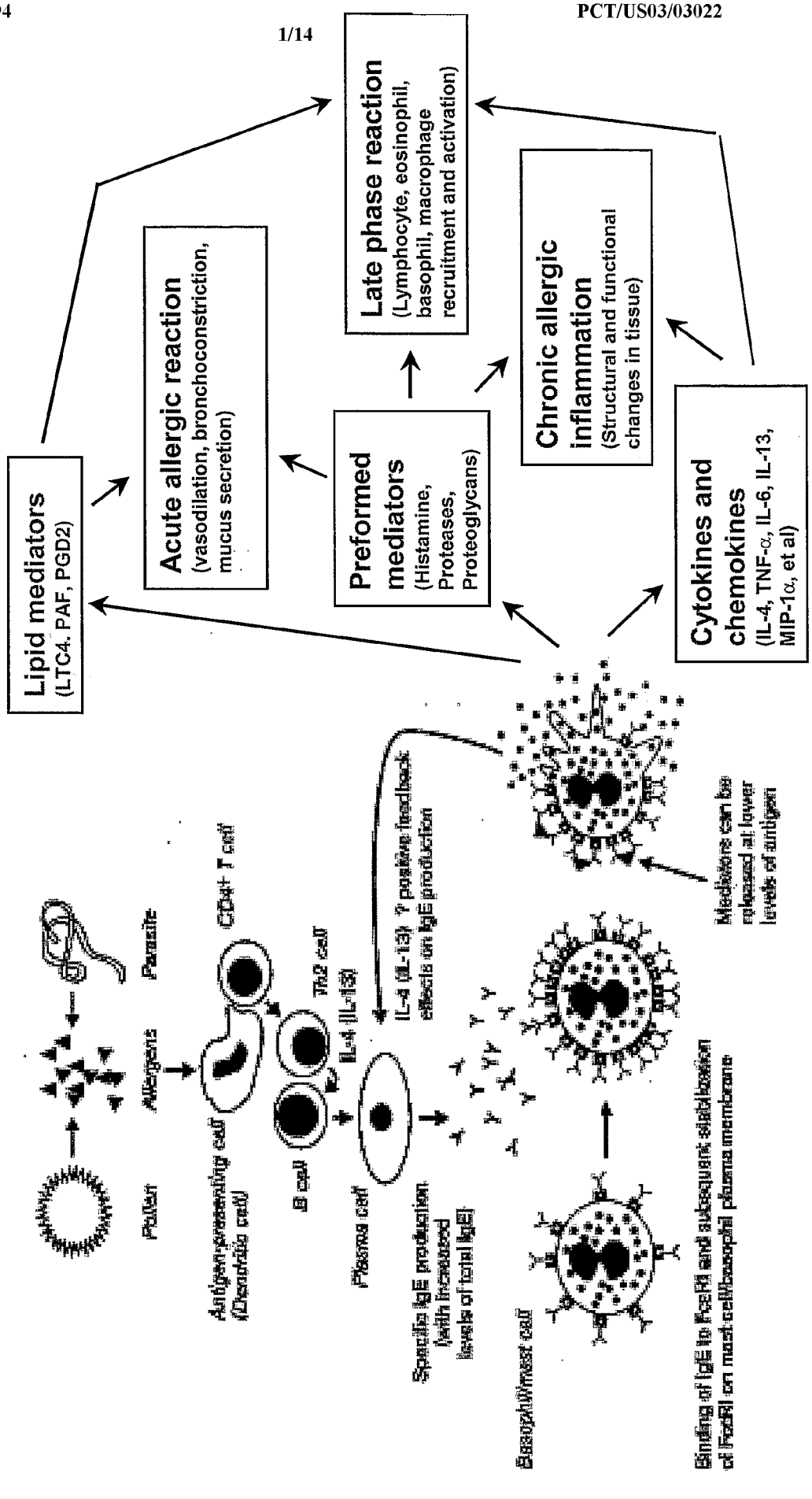

Lipid mediators
(LTC4. PAF, PGD2)
Acute allergic reaction
(vasodilation, bronchoconstriction, mucus secretion)
Preformed mediators
(Histamine, Proteases, Proteoglycans)
Late phase reaction
(Lymphocyte, eosinophil, basophil, macrophage recruitment and activation)
Chronic allergic inflammation
(Structural and functional changes in tissue)
Cytokines and chemokines
(IL-4, TNF-α, IL-6, IL-13, MIP-1α, et al)
Pollen
Allergens
Parasite
Antigen-presenting cell (Dendritic cell)
CD4+ T cell
B cell
Th2 cell
IL-4 (IL-13)
Plasma cell
IL-4 (IL-13) ? positive-feedback effects on IgE production
Specific IgE production (with increased levels of total IgE)
Basophil/mast cell
Binding of IgE to FcεRI and subsequent stabilization of FcεRI on mast cell/basophil plasma membrane
Mediators can be released at lower levels of antigen

FIG. 2

Mast Cell FceR1 Signaling Pathway

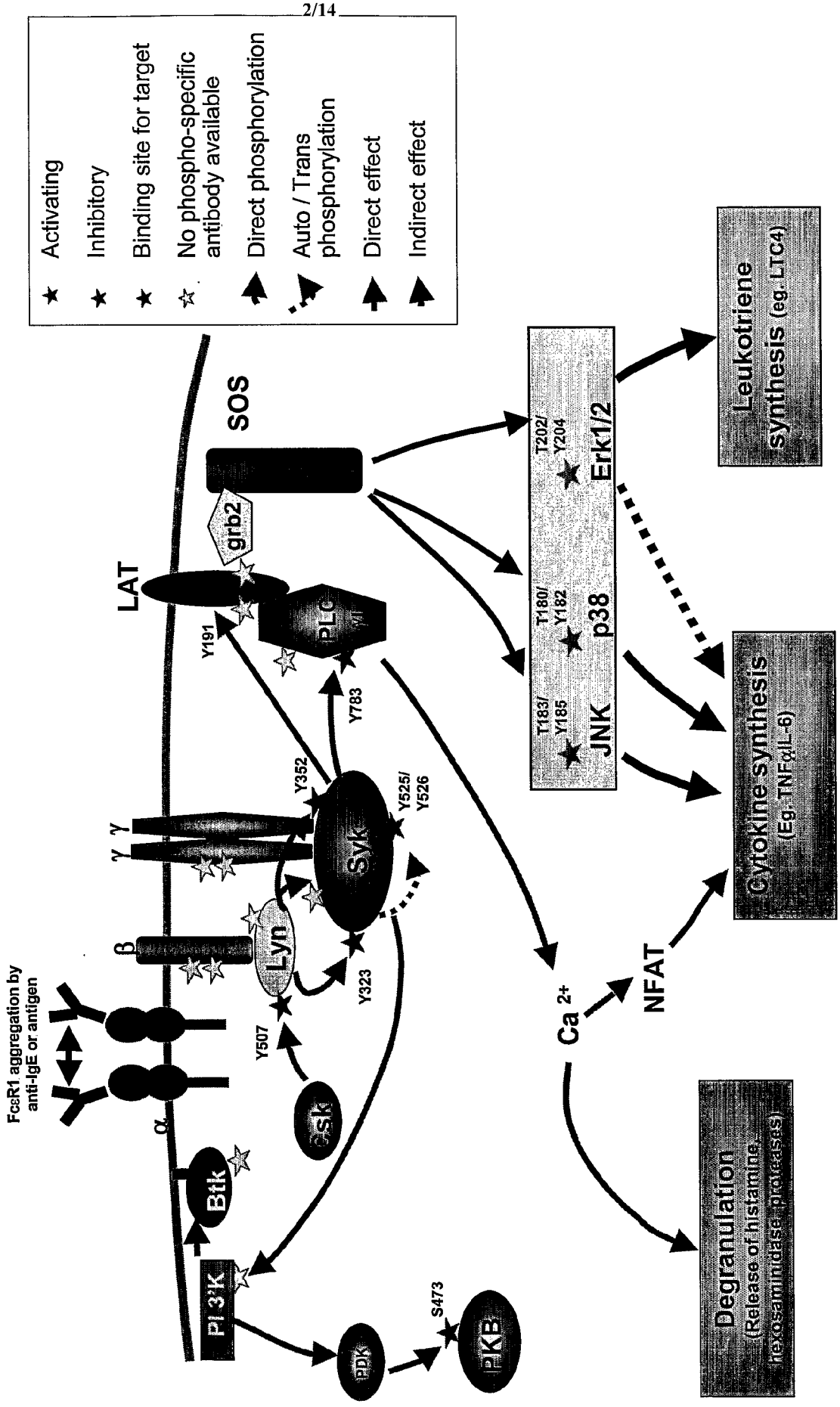


FIG. 3

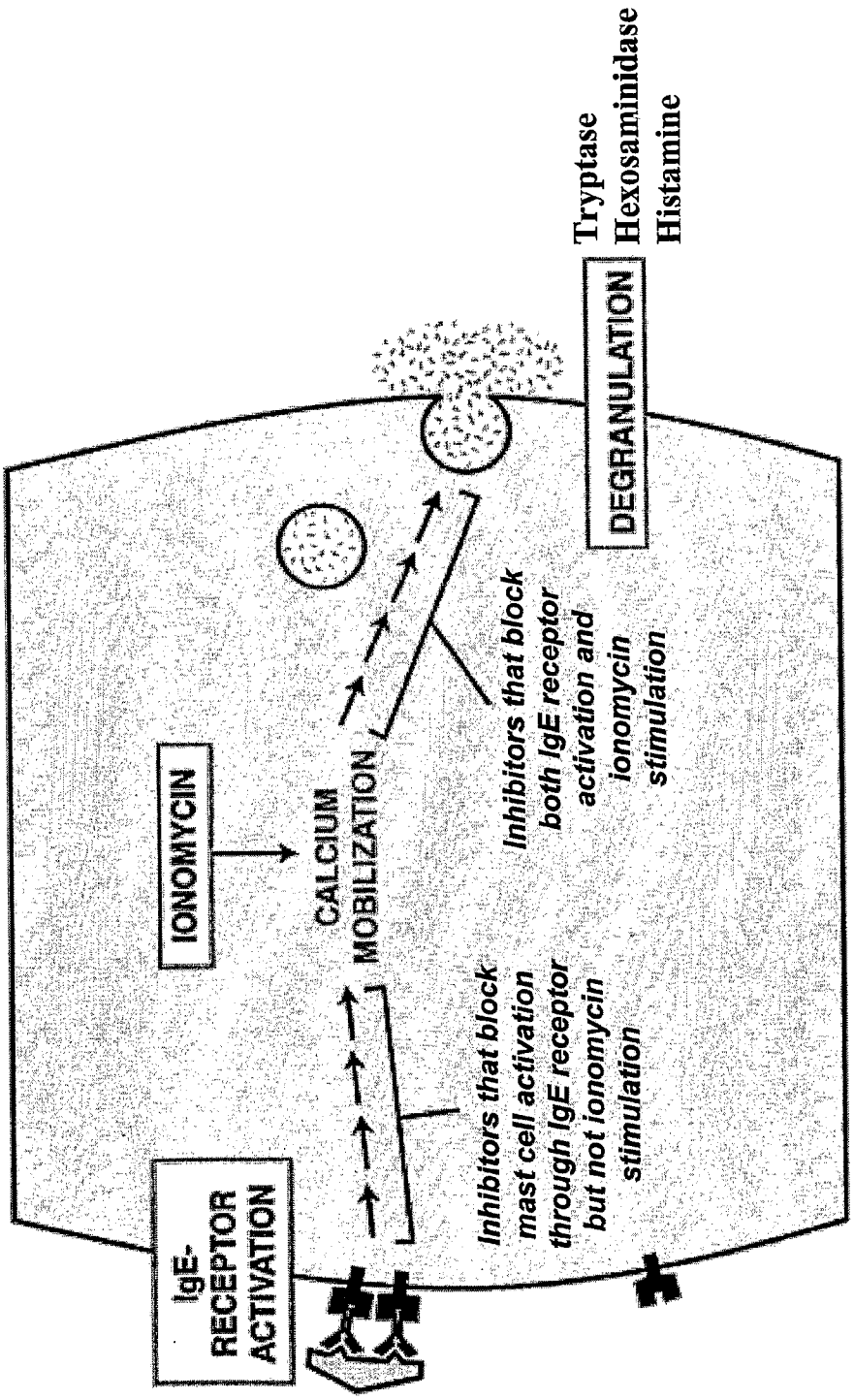

Crosslinking of IgE
with anti-IgE antibody
IgE-
RECEPTOR
ACTIVATION
IONOMYCIN
CALCIUM
MOBILIZATION
DEGRANULATION
Tryptase
Hexosaminidase
Histamine
Inhibitors that block
mast cell activation
through IgE receptor
but not ionomycin
stimulation
Inhibitors that block
both IgE receptor
activation and
ionomycin
stimulation

FIG. 4

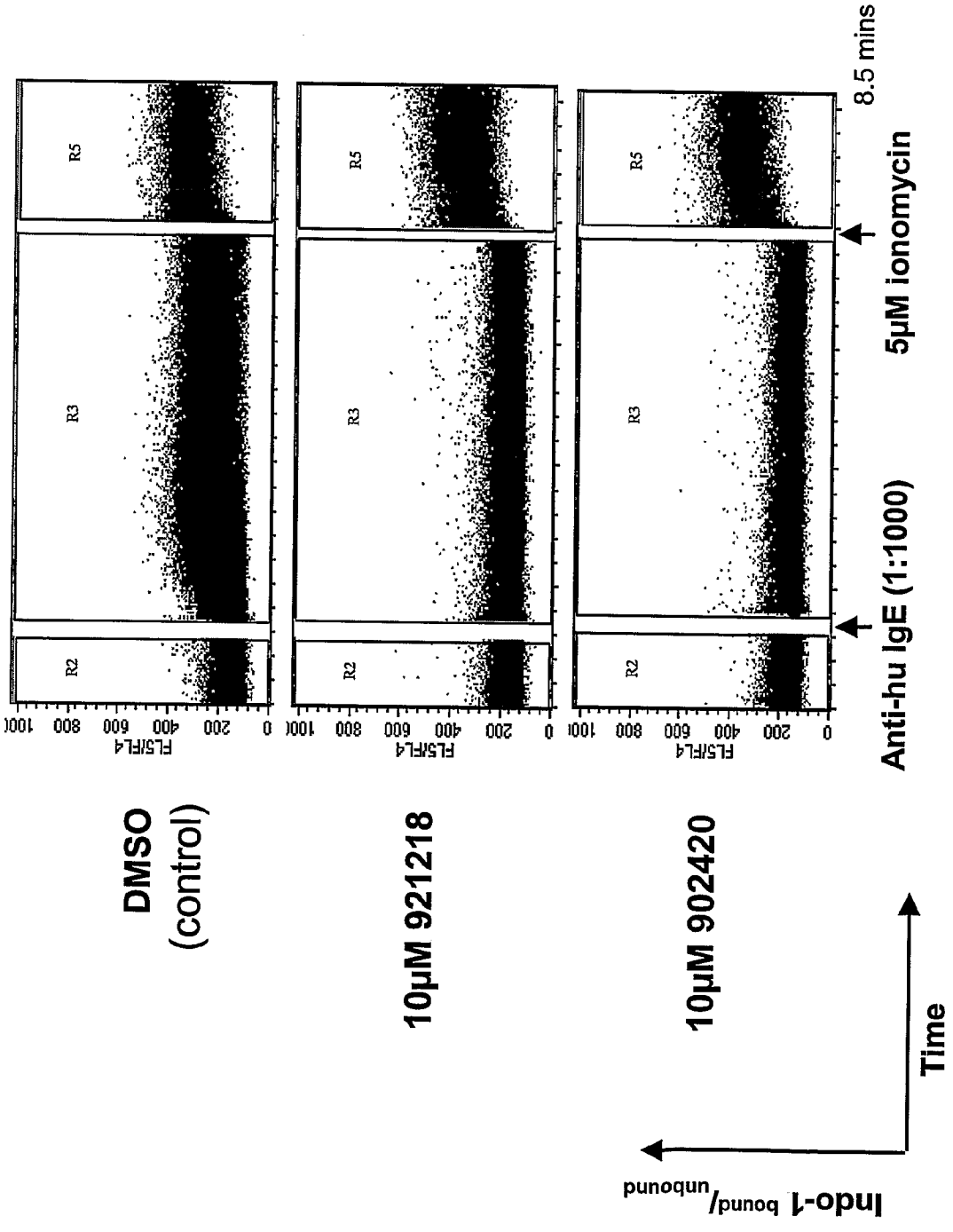

DMSO (control)
10µM 921218
10µM 902420
R2
R3
R5
FL5/FL4
0
200
400
600
800
1000
Anti-hu IgE (1:1000)
5µM ionomycin
8.5 mins
Time
Indo-1 bound/unbound

FIG. 5

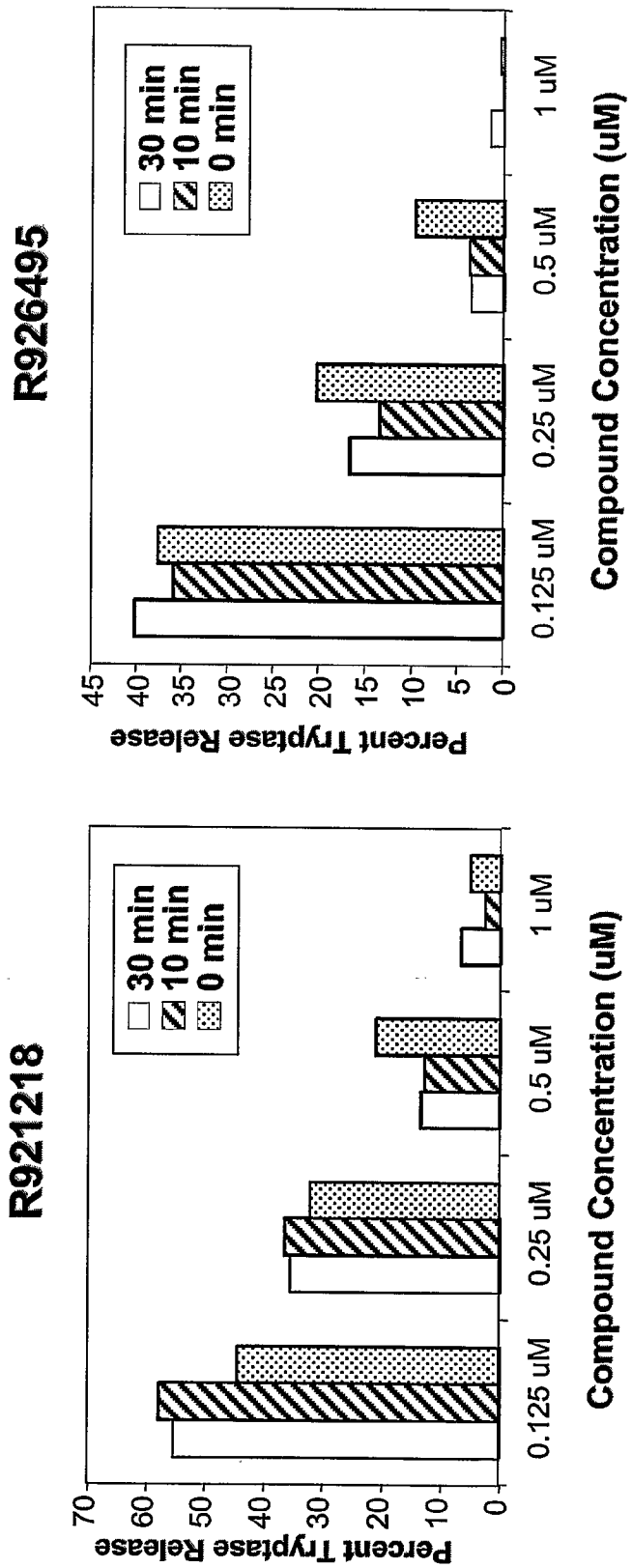

R926495
30 min
10 min
0 min
Percent Tryptase Release
0
5
10
15
20
25
30
35
40
45
0.125 uM
0.25 uM
0.5 uM
1 uM
Compound Concentration (uM)
R921218
30 min
10 min
0 min
Percent Tryptase Release
0
10
20
30
40
50
60
70
0.125 uM
0.25 uM
0.5 uM
1 uM
Compound Concentration (uM)

FIG. 6

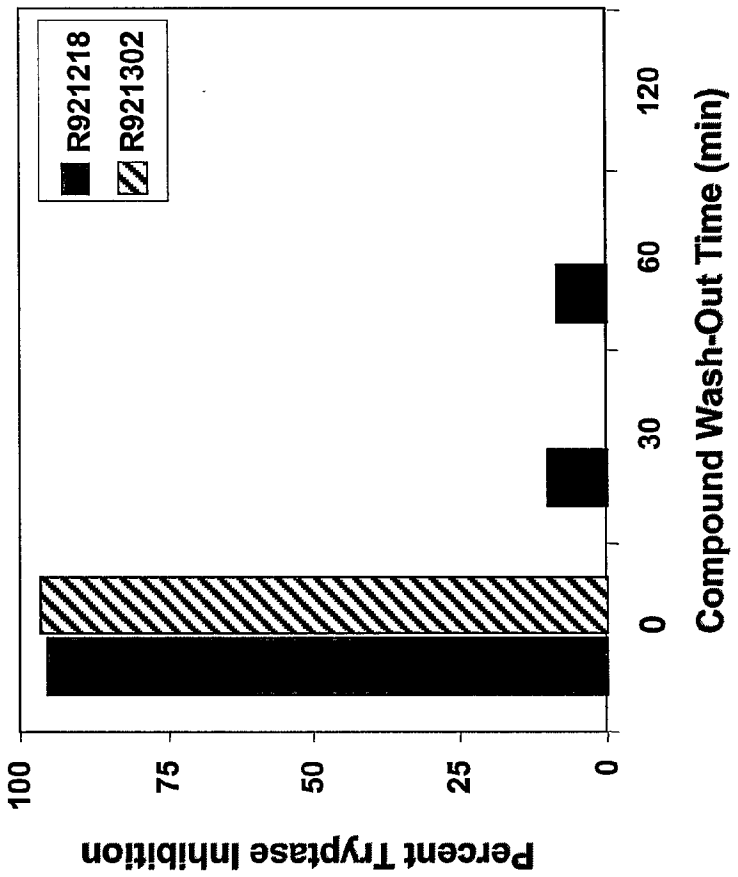

R921218
R921302
Percent Tryptase Inhibition
100
75
50
25
0
0
30
60
120
Compound Wash-Out Time (min)

FIG. 7

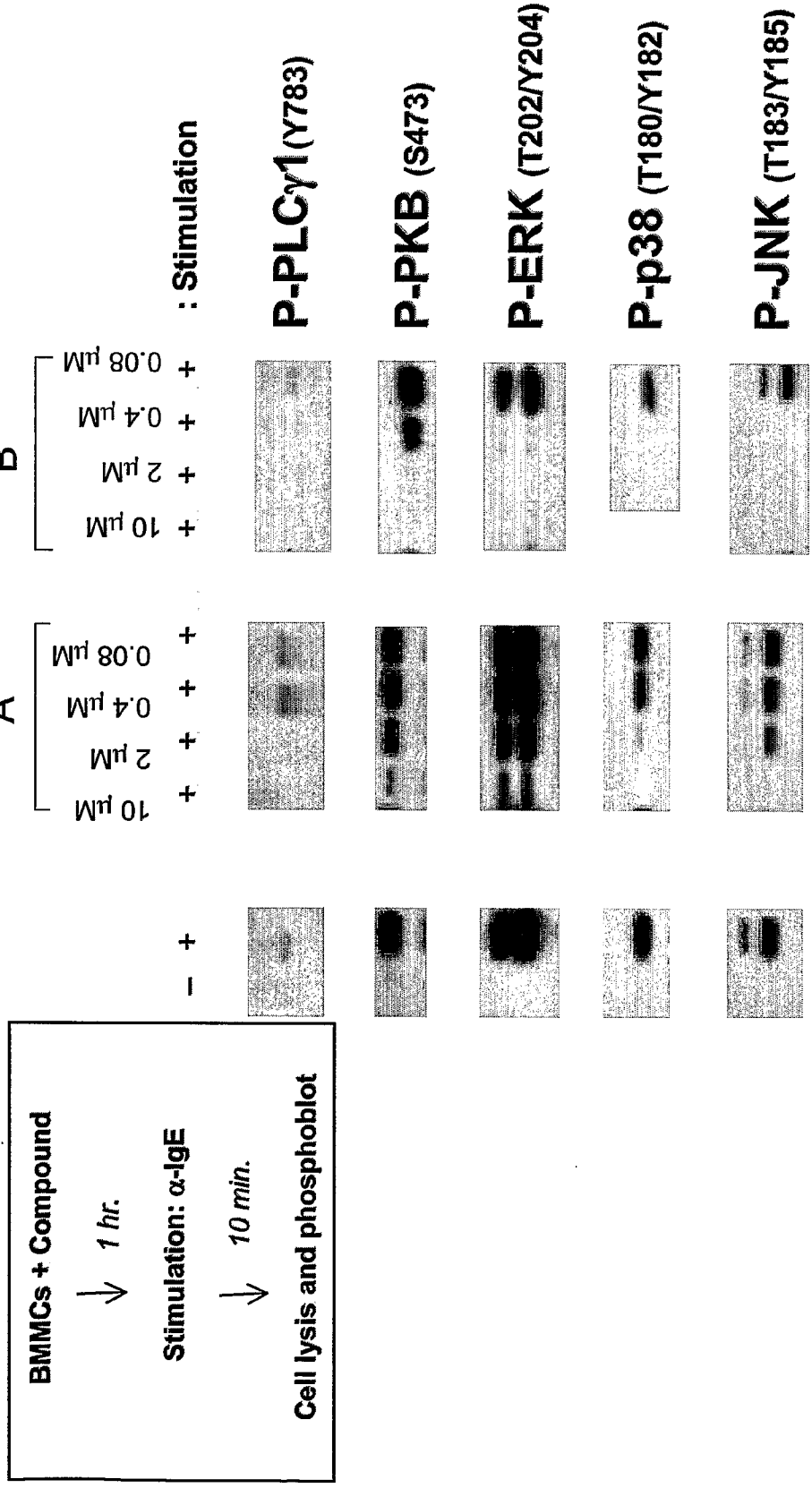
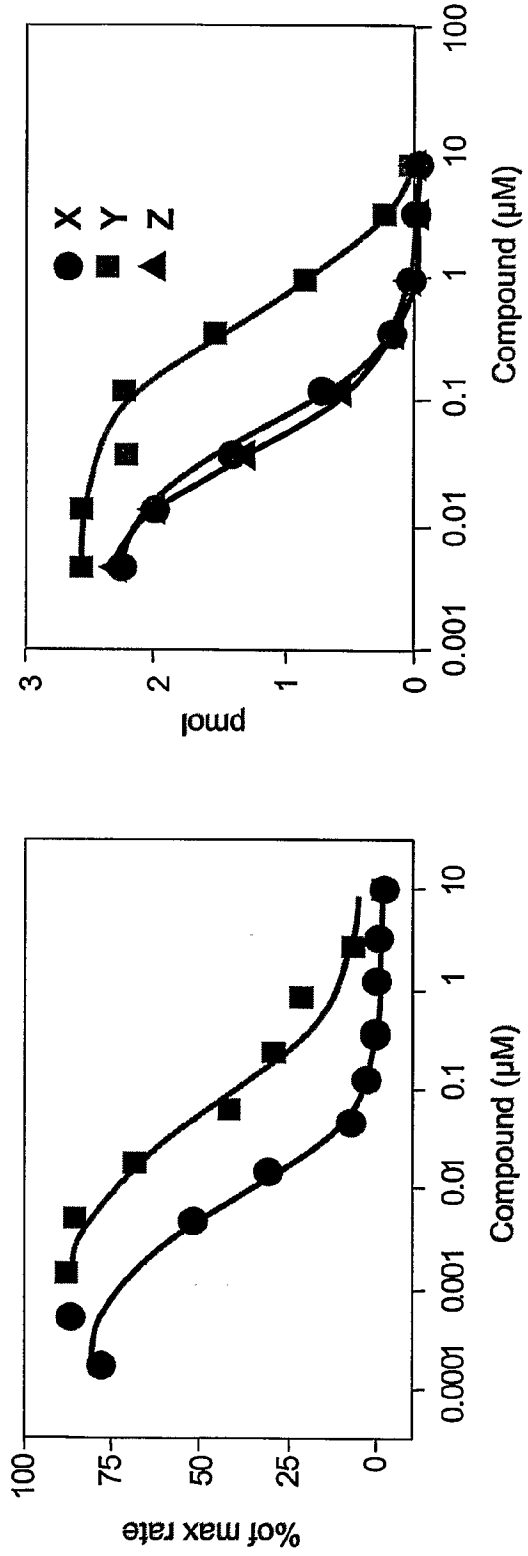

Inhibition of Phosphorylation of Proteins Downstream of Syk Kinase in Fce Receptor Activated BMMC Cells
BMMCs + Compound
1 hr.
Stimulation: α-IgE
10 min.
Cell lysis and phosphoblot
A
B
10 μM
2 μM
0.4 μM
0.08 μM
: Stimulation
P-PLCγ1 (Y783)
P-PKB (S473)
P-ERK (T202/Y204)
P-p38 (T180/Y182)
P-JNK (T183/Y185)

FIG. 8

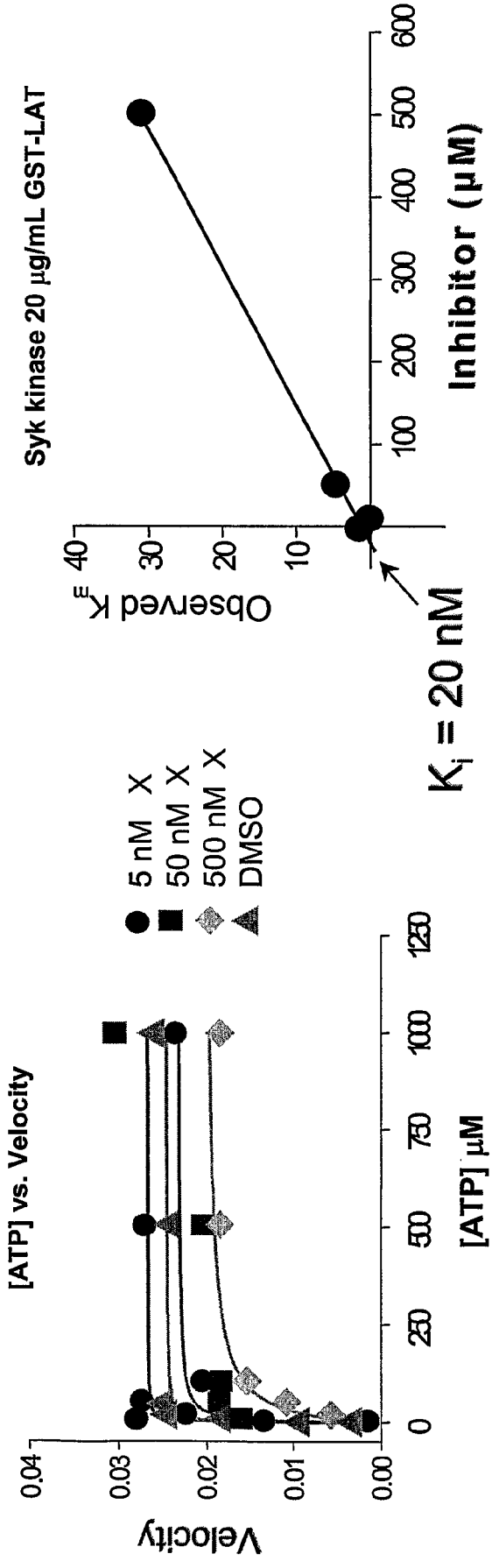
The Disclosed Compounds Potently Inhibit the Activity of Syk Kinase

Human Syk kinase
***In vitro* Fluorescence Polarization Kinase Assay**



	IC_{50} (nM)	
	GST-LAT	HS-1
Y	200	570
X	10	62
Z	ND	43

FIG. 9



	DMSO	5 nM X	50 nM X	500 nM X
V_{max}	.025	0.027	.023	0.020
K_m	1.54	0.79	4.5	31

FIG. 10

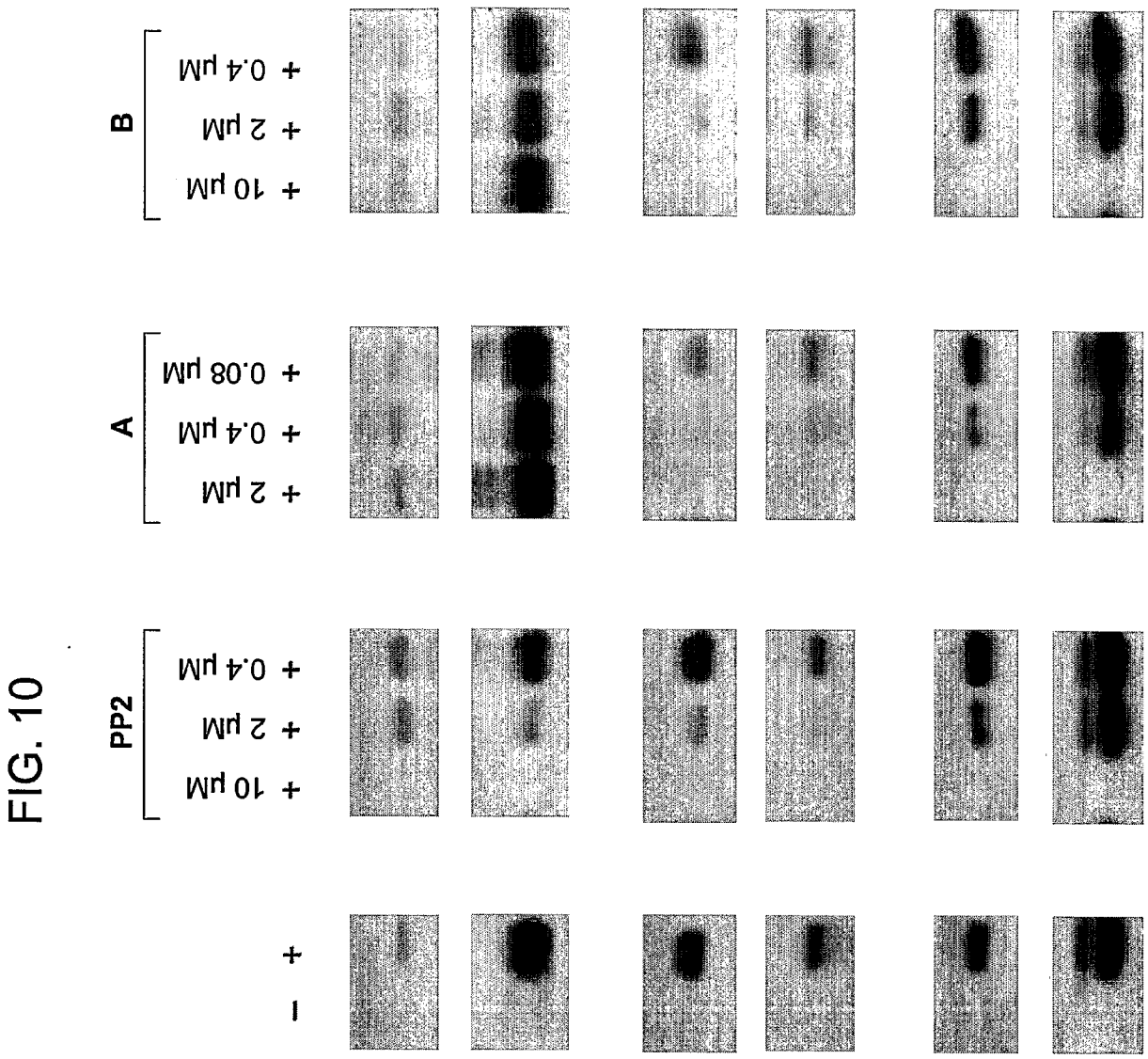

CHMC: Cultured human mast cells
Compound
(1 hour preincubation)
Stimulation: α-IgE
- +
PP2
+ 10 μM
+ 2 μM
+ 0.4 μM
A
+ 2 μM
+ 0.4 μM
+ 0.08 μM
B
+ 10 μM
+ 2 μM
+ 0.4 μM
Lyn Targets
P-Cbl (Y774)
P-Syk (Y352)
Syk Targets
P-LAT (Y191)
P-PLCγ1(Y783)
Indirect Targets
P-PKB (S473)
P-ERK (T202/Y204)

FIG. 11A

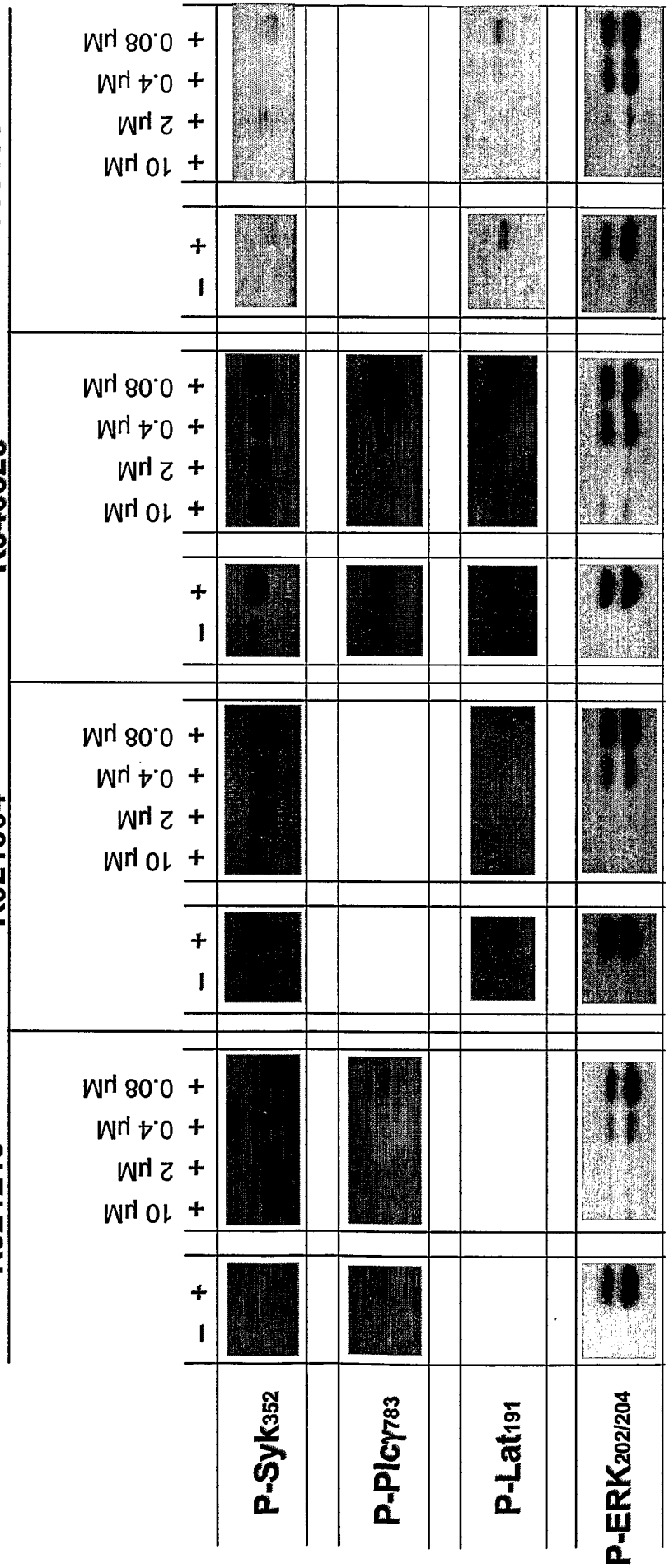

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC
R921219
R921304
R940323
R935138
- + 10 μM + 2 μM + 0.4 μM + 0.08 μM
P-Syk352
P-PlCγ783
P-Lat191
P-ERK202/204

FIG. 11B

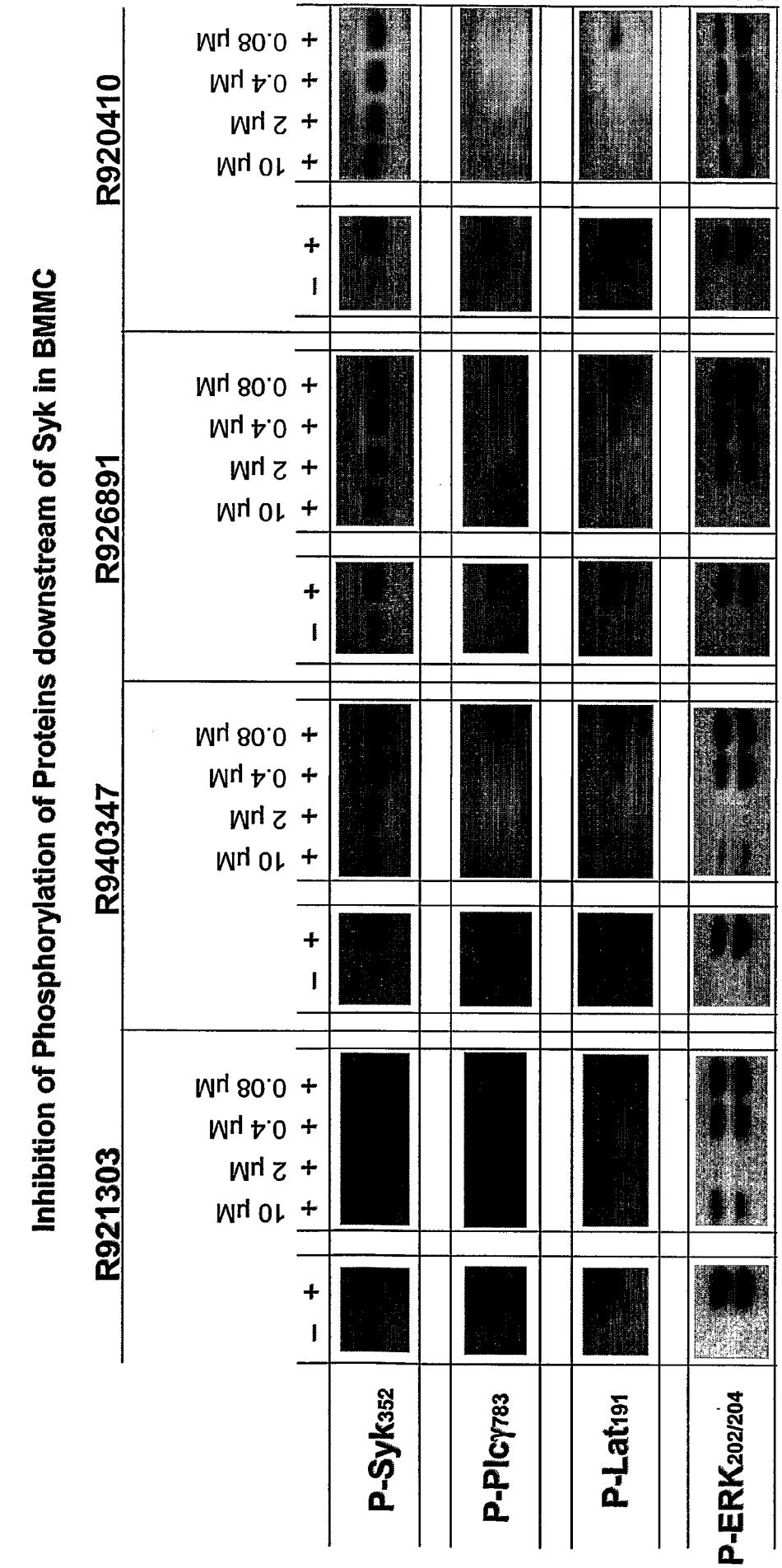

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC
R921303
R940347
R926891
R920410
- 10 µM
+ 2 µM
+ 0.4 µM
+ 0.08 µM
I
+
P-Syk352
P-PlCγ783
P-Lat191
P-ERK202/204

FIG. 11C

Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC

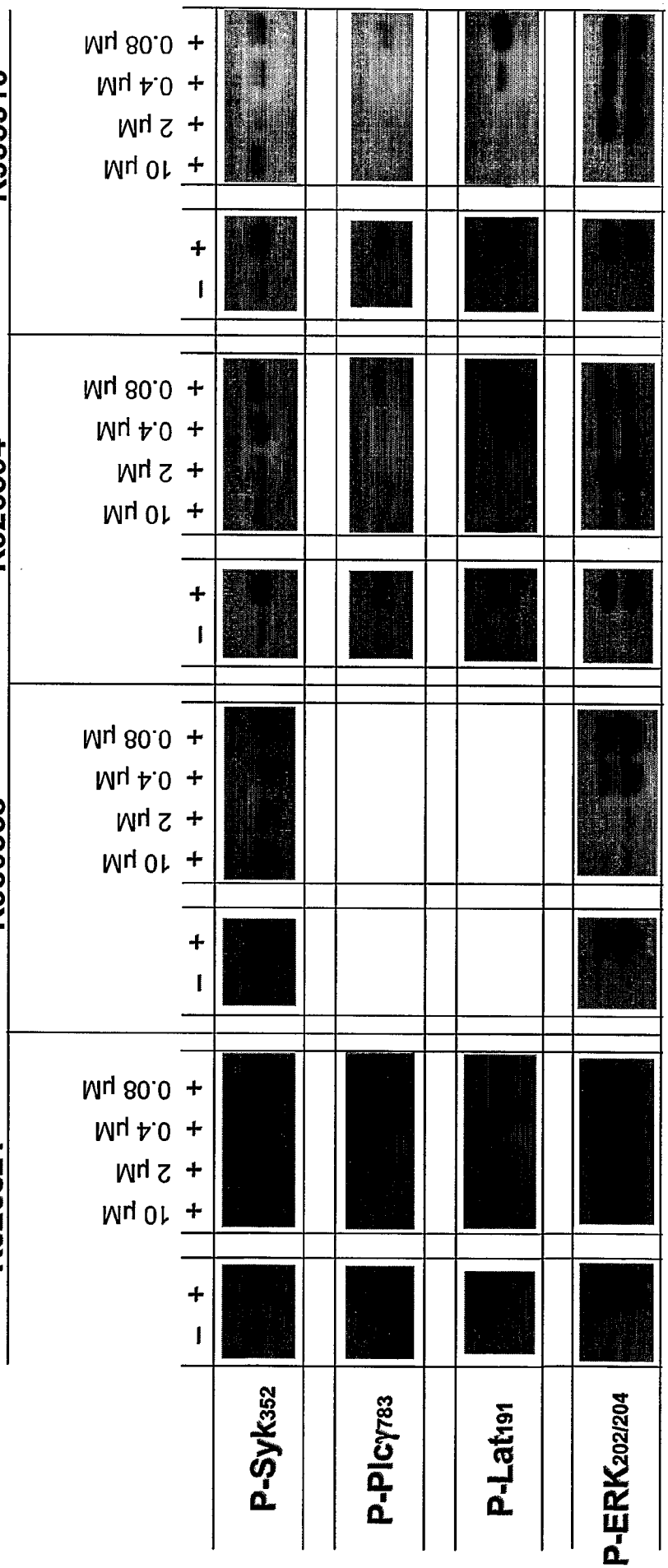
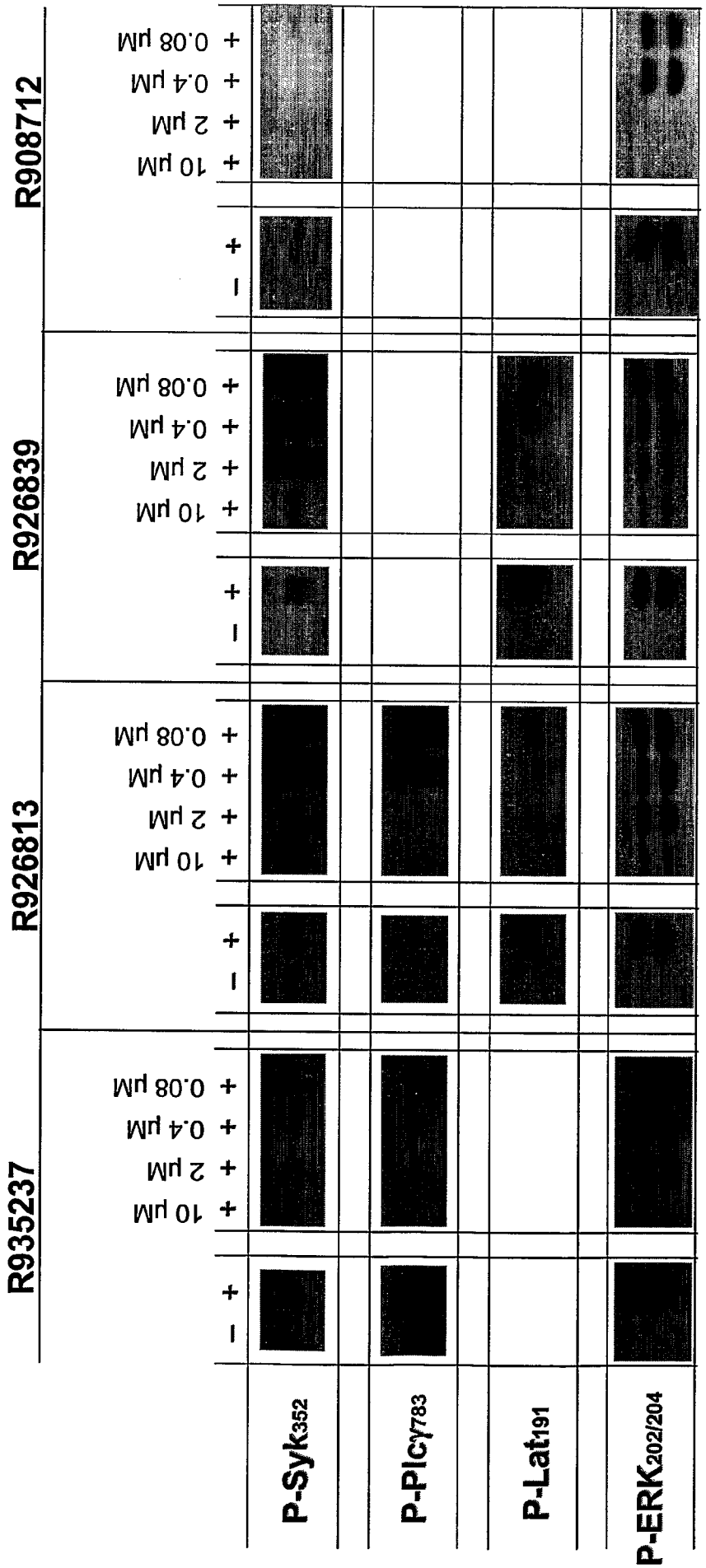


FIG. 11D


Inhibition of Phosphorylation of Proteins downstream of Syk in BMMC
R935237
R926813
R926839
R908712
- + 10 µM + 2 µM + 0.4 µM + 0.08 µM
P-Syk352
P-PlCγ783
P-Lat191
P-ERK202/204